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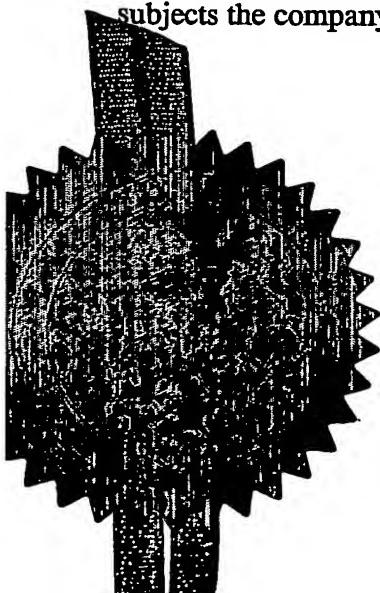
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I also certify that the attached copy of the request for grant of a Patent (Form 1/77) bears an amendment, effected by this office, following a request by the applicant and agreed to by the Comptroller-General.

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Dated 1 September 2004

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1/77

27 OCT 03 E847264-2 D02029  
P01/7700 0.00-0324895.2The Patent Office  
Cardiff Road  
Newport  
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1. Your reference

DES/JW/PB60566P

2. Patent application number

(The Patent Office will fill in his part)

0324895.2

3. Full name, address and postcode of the or of each applicant (*underline all surnames*)Glaxo Group Limited  
Glaxo Wellcome House, Berkeley Avenue,  
Greenford, Middlesex UB6 0NN, Great BritainPatents ADP number (*if you know it*)

473587003

United Kingdom

If the applicant is a corporate body, give the country/state of its incorporation

4. Title of the invention

Compounds

5. Name of your agent (*if you have one*)

Corporate Intellectual Property

"Address for service" in the United Kingdom to which all correspondence should be sent  
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Corporate Intellectual Property (CN9 25.1)  
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BRENTFORD  
Middlesex TW8 9GSPatents ADP number (*if you know it*)

8072555006

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(*if you know it*)      (day / month / year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application      Date of filing  
(*day / month / year*)8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (*Answer yes if:*

- a) any applicant named in part 3 is not an inventor, or
- b) there is an inventor who is named as an applicant, or
- c) any named applicant is a corporate body

See note (d)

# Patents Form 1/77

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Continuation sheets of this form

Description

53

Claim(s)

1

Abstract

Drawings

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10. If you are also filing any of the following, state how many against each item.

Priority Documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (*Patents Form 7/77*)

Request for preliminary examination and search (*Patents Form 9/77*)

Request for substantive examination  
(*Patents Form 10/77*)

Any other documents  
(please specify)

11.

We request the grant of a patent on the basis of this application

Signature

K Rutter

Date 24-Oct-03

12. Name and daytime telephone number of person to contact in the United Kingdom

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COMPOUNDS

This invention relates to heterocyclic compounds, to processes for their preparation, to pharmaceutical compositions containing them and to their use in medicine, in particular  
5 their use in the treatment of conditions mediated by the action of PGE<sub>2</sub> at the EP<sub>1</sub> receptor and conditions mediated by the action of thromboxane on the TP receptor. The invention also relates to compounds having activity at both the EP<sub>1</sub> and TP receptors.

The EP<sub>1</sub> receptor is a 7-transmembrane receptor and its natural ligand is the prostaglandin  
10 PGE<sub>2</sub>. PGE<sub>2</sub> also has affinity for the other EP receptors (types EP<sub>2</sub>, EP<sub>3</sub> and EP<sub>4</sub>). The EP<sub>1</sub> receptor is associated with smooth muscle contraction, pain (in particular inflammatory, neuropathic and visceral), inflammation, allergic activities, renal regulation and gastric or enteric mucus secretion. We have now found a novel group of compounds which bind with high affinity to the EP<sub>1</sub> receptor.

15 A number of review articles describe the characterization and therapeutic relevance of the prostanoid receptors as well as the most commonly used selective agonists and antagonists: *Eicosanoids; From Biotechnology to Therapeutic Applications*, Folco, Samuelsson, Maclouf, and Velo eds, Plenum Press, New York, 1996, chap. 14, 137-154 and *Journal of Lipid Mediators and Cell Signalling*, 1996, 14, 83-87 and *Prostanoid Receptors, Structure, Properties and Function*, S Narumiya et al, *Physiological Reviews* 1999, 79(4), 1193-126. An article from *The British Journal of Pharmacology*, 1994, 112, 735- 740 suggests that Prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) exerts allodynia through the EP<sub>1</sub> receptor subtype and hyperalgesia through EP<sub>2</sub> and EP<sub>3</sub> receptors in the mouse spinal cord. Furthermore an article from *The 20 Journal of Clinical Investigation*, 2001, 107 (3), 325 shows that in the EP<sub>1</sub> knock-out mouse pain-sensitivity responses are reduced by approximately 50%. Two papers from *Anesthesia and Analgesia* have shown that (2001, 93, 1012-7) an EP<sub>1</sub> receptor antagonist (ONO-8711) reduces hyperalgesia and allodynia in a rat model of chronic constriction injury, and that (2001, 92, 233-238) the same antagonist inhibits mechanical hyperalgesia in a rodent model 25 of post-operative pain. S. Sarkar et al in *Gastroenterology*, 2003, 124(1), 18-25 demonstrate the efficacy of EP<sub>1</sub> receptor antagonists in the treatment of visceral pain in a human model of hypersensitivity. Thus, selective prostaglandin ligands, agonists or antagonists, depending on which prostaglandin E receptor subtype is being considered, have anti-inflammatory, antipyretic and analgesic properties similar to a conventional non-steroidal anti-inflammatory drug, and in addition, inhibit hormone-induced uterine contractions and have anti-cancer 30 effects. These compounds have a diminished ability to induce some of the mechanism-based side effects of NSAIDs which are indiscriminate cyclooxygenase inhibitors. In particular, the compounds have a reduced potential for gastrointestinal toxicity, a reduced potential for renal side effects, a reduced effect on bleeding times and a lessened ability to induce asthma attacks in aspirin-sensitive asthmatic subjects. Moreover, by sparing potentially beneficial prostaglandin pathways, these agents may have enhanced efficacy over NSAIDS and/or 35 COX-2 inhibitors.

Certain compounds of the present invention also exhibit antagonism at the TP receptor.

5       The TP (also known as TxA<sub>2</sub>) receptor is a prostanoid receptor subtype stimulated by the endogenous mediator thromboxane. Activation of this receptor results in various physiological actions primarily incurred by its platelet aggregatory and smooth muscle constricting effects, thus opposing those of prostacyclin receptor activation.

10      TP receptors have been identified in human kidneys (G.P. Brown *et al*, *Prostaglandins and other lipid mediators*, 1999, 57, 179-188) in the glomerulus and extraglomerular vascular tissue. Activation of TP receptors constricts glomerular capillaries and suppresses glomerular filtration rates (M.D. Breyer *et al*, *Current Opinion in Nephrology and Hypertension*, 2000, 9, 23-29), indicating that TP receptor antagonists could be useful for renal dysfunction in glomerulonephritis, diabetes mellitus and sepsis.

15      Activation of TP receptors induces bronchoconstriction, increase in microvascular permeability, formation of mucosal oedema and mucus secretion, typical characteristic features of bronchial asthma (T. Obata *et al*, *Clinical Review of Allergy*, 1994, 12(1), 79-93). TP antagonists have been investigated as potential asthma treatments resulting in, 20     for example, orally active Seratrodast (AA-2414) (S. Terao *et al*, *Yakugaku Zasshi*, 1999, 119(5), 377-390). Ramatroban is another TP receptor antagonist currently undergoing phase III clinical trials as an anti-asthmatic compound.

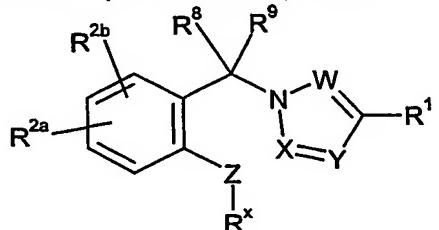
25      Antagonists at the TP receptor have been shown to have a gastroprotective effect. In rats it has been shown that SQ 33961 and BM 13505 inhibit gastric lesions induced by taurocholate acid, aspirin or indomethacin (E.H. Ogletree *et al*, *Journal of Pharmacology and Experimental Therapeutics*, 1992, 263(1), 374-380).

30      In The American Physiological Society (1994, 267, R289-R-294), studies suggest that PGE<sub>2</sub>-induced hyperthermia in the rat is mediated predominantly through the EP<sub>1</sub> receptor. WO 96/06822 (March 7, 1996), WO 96/11902 (April 25, 1996), EP 752421-A1 (January 08, 1997) and WO 01/19814 (22 March 2001) disclose compounds as being useful in the treatment of prostaglandin mediated diseases.

35      It is now suggested that a novel group of pyrazole derivatives surprisingly are selective for the EP<sub>1</sub> receptor over the EP<sub>3</sub> receptor, and are therefore indicated to be useful in treating conditions mediated by the action of PGE<sub>2</sub> at EP<sub>1</sub> receptors. Such conditions include pain, or inflammatory, immunological, bone, neurodegenerative or renal disorders.

40      It is also suggested that this novel group of pyrazole derivatives are antagonists at the TP receptor and are therefore indicated to be useful in treating conditions mediated by the action of thromboxane at the TP receptor. Such conditions include renal disorders, asthma and gastric lesions.

Accordingly the present invention provides compounds of formula (I):



(I)

wherein:

- 5    W represents N or CR<sup>10</sup> wherein R<sup>10</sup> represents hydrogen, halogen, optionally substituted alkyl, optionally substituted aryl, or optionally substituted heterocyclyl;
- X represents N or CR<sup>11</sup> wherein R<sup>11</sup> represents hydrogen, halogen, optionally substituted alkyl, optionally substituted aryl, or optionally substituted heterocyclyl;
- Y represents N or CR<sup>12</sup> wherein R<sup>12</sup> represents hydrogen, halogen, CH<sub>3</sub> or CF<sub>3</sub>;
- 10    Z represents O, S, SO or SO<sub>2</sub>;  
R<sup>1</sup> represents CO<sub>2</sub>R<sup>4</sup>, CONR<sup>5</sup>R<sup>6</sup>, CH<sub>2</sub>CO<sub>2</sub>H, optionally substituted SO<sub>2</sub>alkyl, SO<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>, NR<sup>5</sup>CONR<sup>5</sup>R<sup>6</sup>, 2H-tetrazol-5-yl-methyl or optionally substituted heterocyclyl;
- 15    R<sup>2a</sup> and R<sup>2b</sup> independently represents hydrogen, halo, optionally substituted alkyl, optionally substituted alkoxy, CN, SO<sub>2</sub>alkyl, SR<sup>5</sup>, NO<sub>2</sub>, optionally substituted aryl, CONR<sup>5</sup>R<sup>6</sup> or optionally substituted heteroaryl;
- R<sup>x</sup> represents optionally substituted alkyl wherein 1 or 2 of the non-terminal carbon atoms are optionally replaced by a group independently selected from NR<sup>4</sup>, O and SO<sub>n</sub>, wherein n is 0, 1 or 2; or R<sup>x</sup> represents optionally substituted CQ<sup>a</sup>Q<sup>b</sup>-heterocyclyl, optionally substituted CQ<sup>a</sup>Q<sup>b</sup>-bicyclic heterocyclyl or optionally substituted CQ<sup>a</sup>Q<sup>b</sup>-aryl;
- 20    R<sup>4</sup> represents hydrogen or an optionally substituted alkyl;  
R<sup>5</sup> represents hydrogen or an optionally substituted alkyl;  
R<sup>6</sup> represents hydrogen or optionally substituted alkyl, optionally substituted heteroaryl, optionally substituted SO<sub>2</sub>aryl, optionally substituted SO<sub>2</sub>alkyl, optionally substituted SO<sub>2</sub>heteroaryl, CN, optionally substituted CQ<sup>a</sup>Q<sup>b</sup>aryl, optionally substituted
- 25    CQ<sup>a</sup>Q<sup>b</sup>heteroaryl or COR<sup>7</sup>;  
R<sup>7</sup> represents hydrogen, optionally substituted alkyl, optionally substituted heteroaryl or optionally substituted aryl;
- R<sup>8</sup> and R<sup>9</sup> are independently selected from hydrogen, fluorine or alkyl, or R<sup>8</sup> and R<sup>9</sup> together with the carbon to which they are attached form a cycloalkyl ring, optionally containing up to one heteroatom selected from O, S, NH or N-alkyl;
- 30    wherein Q<sup>a</sup> and Q<sup>b</sup> are each independently selected from hydrogen, CH<sub>3</sub> and fluorine; or derivatives thereof.

Suitable examples of the five membered ring comprising W, X and Y are pyrrole, pyrazole, tetrazole, 2H-1,2,3-triazole and 1,2,4-triazole. Particular examples include pyrrole and pyrazole.

Suitably W is CH.

Suitably X includes CCH<sub>3</sub>, CH and C-thienyl.

5 Suitably Y includes CH and CF.

Preferably R<sup>1</sup> represents CO<sub>2</sub>R<sup>4</sup>. More preferably R<sup>1</sup> represents CO<sub>2</sub>H.

A particular example of Z is O.

10 When R<sup>x</sup> represents optionally substituted alkyl this group is preferably C<sub>1-6</sub>alkyl, for example butyl or *iso*-butyl.

15 When R<sup>x</sup> represents optionally substituted CQ<sup>a</sup>Q<sup>b</sup>-heterocycl, optionally substituted CQ<sup>a</sup>Q<sup>b</sup>-bicyclic heterocycl or optionally substituted CQ<sup>a</sup>Q<sup>b</sup>-aryl, suitably R<sup>x</sup> includes optionally substituted CH<sub>2</sub>-heterocycl e.g. CH<sub>2</sub>-pyridyl, optionally substituted CH<sub>2</sub>-bicyclic heterocycl or optionally substituted CH<sub>2</sub>-aryl e.g. optionally substituted CH<sub>2</sub>-phenyl. Optional substituents for CH<sub>2</sub>-phenyl include one, two or three, preferably one or two substituents selected from Cl, Br, F, CF<sub>3</sub>, NO<sub>2</sub>, C<sub>1-4</sub>alkyl and OC<sub>1-4</sub>alkyl.

20 Suitably R<sup>4</sup> includes hydrogen and C<sub>1-6</sub>alkyl.

Suitably R<sup>5</sup> includes hydrogen and C<sub>1-6</sub>alkyl.

25 Suitably R<sup>6</sup> includes hydrogen and C<sub>1-6</sub>alkyl.

Suitably R<sup>7</sup> includes hydrogen and C<sub>1-6</sub>alkyl.

Suitably R<sup>8</sup> includes hydrogen.

30 Suitably R<sup>9</sup> includes CH<sub>3</sub> and hydrogen.

Suitably R<sup>10</sup> include hydrogen.

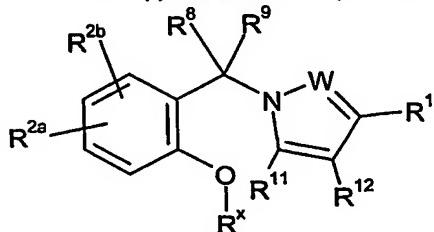
35 Suitably R<sup>11</sup> includes hydrogen, CH<sub>3</sub> and heterocycl, e.g. thienyl.

Suitably R<sup>12</sup> includes hydrogen, halo, e.g. fluorine.

An example of Q<sup>a</sup> is hydrogen.

40 An example of Q<sup>b</sup> is hydrogen.

In one aspect, compounds of formula (I) include compounds of formula (Ia):



(Ia)

wherein:

W is N or CR<sup>10</sup>;

5 R<sup>1</sup> is CO<sub>2</sub>H;

R<sup>2a</sup> and R<sup>2b</sup> are independently selected from hydrogen, halo, optionally substituted C<sub>1-6</sub>alkyl e.g. C<sub>1-4</sub>alkyl and CF<sub>3</sub>, and OC<sub>1-6</sub>alkyl;

R<sup>x</sup> is selected from CH<sub>2</sub>-pyridyl, C<sub>1-6</sub>alkyl or CH<sub>2</sub>Ph wherein Ph is substituted by R<sup>3a</sup>, R<sup>3b</sup> and R<sup>3c</sup>;

10 R<sup>3a</sup>, R<sup>3b</sup> and R<sup>3c</sup> are independently selected from hydrogen, halo, NO<sub>2</sub>, optionally substituted C<sub>1-6</sub>alkoxy, e.g OCH<sub>3</sub> and optionally substituted C<sub>1-6</sub>alkyl, e.g CH<sub>3</sub> and CF<sub>3</sub>; R<sup>8</sup> and R<sup>9</sup> are independently selected from hydrogen, fluorine or C<sub>1-3</sub>alkyl, or R<sup>8</sup> and R<sup>9</sup> together with the carbon to which they are attached form a C<sub>3-6</sub>cycloalkyl ring, optionally containing up to one heteroatom selected from O, S, NH or N-C<sub>1-6</sub>alkyl;

15 R<sup>10</sup> is selected from hydrogen, halogen, and optionally substituted C<sub>1-8</sub>alkyl e.g CH<sub>3</sub> and CF<sub>3</sub>;

R<sup>11</sup> is selected from hydrogen, halogen, optionally substituted C<sub>1-8</sub>alkyl e.g. Me and CF<sub>3</sub> and heterocyclyl e.g. thieryl; and

20 R<sup>12</sup> is selected from hydrogen, halogen e.g. fluorine, and optionally substituted alkyl e.g. CH<sub>3</sub> and CF<sub>3</sub>; or derivatives thereof.

Compounds of formula (I) include the compounds of examples 1 to 62 and derivatives thereof.

25 Preferably compounds are selective for EP<sub>1</sub> over EP<sub>3</sub>. More preferably the compounds are 100 fold selective, more preferably 1000 fold selective for EP<sub>1</sub> over EP<sub>3</sub>.

Derivatives of the compounds of formula (I) include pharmaceutically acceptable derivatives.

30 The invention is described using the following definitions unless otherwise indicated.

The term "pharmaceutically acceptable derivative" means any pharmaceutically acceptable salt, ester, salt of such ester or solvate of the compounds of formula (I), or any

other compound which upon administration to the recipient is capable of providing (directly or indirectly) a compound of formula (I).

- 5 It will be appreciated by those skilled in the art that the compounds of formula (I) may be modified to provide pharmaceutically acceptable derivatives thereof at any of the functional groups in the compounds, and that the compounds of formula (I) may be derivatised at more than one position.

Pharmaceutically acceptable salts include those described by Berge, Bighley and Monkhouse, *J. Pharm. Sci.*, 1977, 66, 1-19. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particular examples include the ammonium, calcium, magnesium, 15 potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, 20 N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropyl amine, tromethamine, and the like. When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, 25 ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acid.

30 Preferred examples of pharmaceutically acceptable salts include those formed from maleic, fumaric, benzoic, ascorbic, pamoic, succinic, bismethylenesalicylic, methanesulfonic, ethanesulfonic, propionic, tartaric, salicylic, citric, gluconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, 35 cyclohexylsulfamic, phosphoric and nitric acids.

The salts and/or solvates of the compounds of the formula (I) which are not pharmaceutically acceptable may be useful as intermediates in the preparation of pharmaceutically acceptable salts and/or solvates of compounds of formula (I) or the 40 compounds of the formula (I) themselves, and as such form another aspect of the present invention.

The compounds of formula (I) may be prepared in crystalline or non-crystalline form, and if crystalline, may be optionally hydrated or solvated. This invention includes in its scope stoichiometric hydrates as well as compounds containing variable amounts of water.

- 5 Suitable solvates include pharmaceutically acceptable solvates, such as hydrates.

Solvates include stoichiometric solvates and non-stoichiometric solvates.

The terms "halogen" or "halo" are used to represent fluorine, chlorine, bromine or iodine.

- 10 The term "alkyl" means a straight, branched or cyclic chain alkyl group or combinations thereof, for example a methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, pentyl, hexyl, 1,1-dimethylethyl, cyclopentyl or cyclohexyl or combinations thereof such as cyclohexylmethyl and cyclopentylmethyl. Unless otherwise defined, preferably "alkyl" is C<sub>1</sub>-8alkyl, more preferably "alkyl" is C<sub>1-6</sub>alkyl.
- 15

- 20 The term "alkoxy" means a straight, branched or cyclic chain alkyl group having an oxygen atom attached to the chain, for example a methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy group, pentoxy, hexyloxy group, cyclopentoxy or cyclohexyloxy group. Preferably "alkoxy" is C<sub>1-6</sub> alkoxy.

- 25 The term "heterocycll" as a group or as part of a group means an aromatic or non-aromatic five or six membered ring which contains from 1 to 4 heteroatoms selected from nitrogen, oxygen or sulfur and unsubstituted or substituted by, for example, up to three substituents, preferably one or two substituents. Examples of 5- membered heterocycll groups include furyl, dioxalanyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, triazinyl, isothiazolyl, isoxazolyl, thiophenyl, pyrazolyl or tetrazolyl. Examples of 6-membered heterocycll groups are pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl or tetrazinyl.
- 30

- 35 The term "aryl" as a group or part of a group means a 5- or 6- membered aromatic ring, for example phenyl, or a 7 to 12 membered bicyclic ring system where at least one of the rings is aromatic, for example naphthyl. An aryl group may be optionally substituted by one or more substituents, for example up to 4, 3 or 2 substituents. Preferably the aryl group is phenyl.

- 40 The term "heteroaryl" as a group or as part of a group means a monocyclic five or six membered aromatic ring, or a fused bicyclic aromatic ring system comprising two of such monocyclic five or six membered aromatic rings. These heteroaryl rings contain one or more heteroatoms selected from nitrogen, oxygen or sulfur, where N-oxides, sulfur oxides and sulfur dioxides are permissible heteroatom substitutions. A heteroaryl group may be optionally substituted by one or more substituents, for example up to 3 or up to 2

substituents. Examples of "heteroaryl" used herein include furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, quinolinyl, isoquinolinyl, benzofuryl, benzothienyl, indolyl, and indazolyl.

5

The term "bicyclic heterocyclyl" when used herein means a fused bicyclic aromatic or non-aromatic bicyclic heterocyclyl ring system comprising up to four, preferably one or two, heteroatoms each selected from oxygen, nitrogen and sulphur. Each ring may have from 4 to 7, preferably 5 or 6, ring atoms. A bicyclic heteroaromatic ring system may include a carbocyclic ring. Examples of bicyclic heterocyclyl groups include quinolinyl, isoquinolinyl, quinoxalinyl, quinazolinyl, pyridopyrazinyl, benzoxazolyl, benzothiophenyl, benzimidazolyl, benzothiazolyl, benzoxadiazolyl, benzthiadiazolyl, indolyl, benztriazolyl or naphthyridinyl.

10

When the heteroatom nitrogen replaces a carbon atom in an alkyl group, or when nitrogen is present in a heteroaryl, heterocyclyl or bicyclic heterocyclyl group, the nitrogen atom will, where appropriate be substituted by one or two substituents selected from hydrogen and C<sub>1-8</sub>alkyl, preferably hydrogen and C<sub>1-6</sub>alkyl, more preferably hydrogen.

15

Optional substituents for alkyl groups include OH, CO<sub>2</sub>R<sup>4</sup>, NR<sup>4</sup>R<sup>5</sup>, (O), OC<sub>1-6</sub>alkyl or halo, wherein R<sup>4</sup> and R<sup>5</sup> are as herein before defined for compounds of formula (I). An alkyl group may be substituted by one or more optional substituents, for example up to 5, 4, 3, or 2 optional substituents.

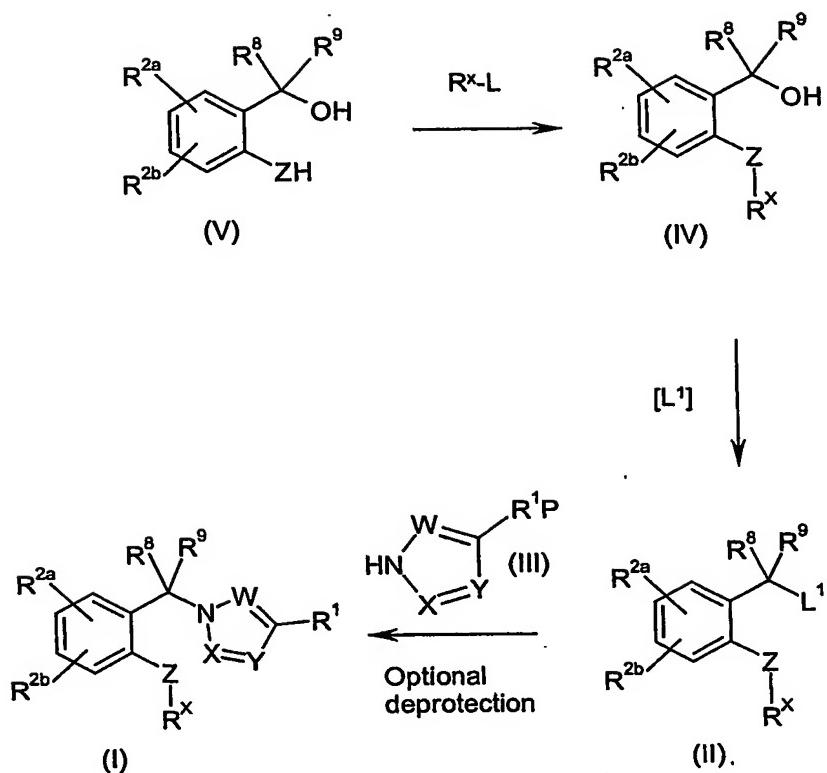
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Unless otherwise defined, optional substituents for aryl, heteroaryl or heterocyclyl moieties as a group or part of a group are selected from optionally substituted C<sub>1-6</sub>alkyl, optionally substituted C<sub>1-6</sub>alkoxy and halogen. Alternative optional substituents include C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy and halogen.

25

Compounds of formula (I) can be prepared as set forth in the following schemes and in the examples. The following processes form another aspect of the present invention.

For example, compounds of formula (I) may be prepared by the general route below:



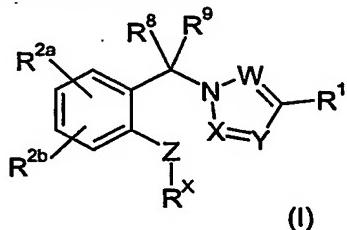
5 wherein L and L<sup>1</sup> are leaving groups, for example halo e.g. bromo; and W, X, Y, Z, R<sup>2a</sup>, R<sup>2b</sup>, R<sup>1</sup>, R<sup>8</sup>, R<sup>9</sup>, and R<sup>x</sup> are as defined for compounds of formula (I), and P is an optional protecting group. The skilled person will recognise when the use of a protecting group is necessary. When R<sup>1</sup> is CO<sub>2</sub>H, R<sup>1</sup>P is suitably CO<sub>2</sub>C<sub>1-4</sub>alkyl or optionally substituted benzyl.

Suitable reaction conditions for the reaction of an amine of formula (III) with a compound of formula (II) to give a compound of formula (I) include heating in a solvent, e.g. ethanol, in the presence of a base, e.g. potassium *tert*-butoxide.

Suitable reaction conditions for the preparation a compound of formula (II) include conventional methods for converting the hydroxy group of the compound of formula (IV) to a leaving group, for example when L<sup>1</sup> is Br, the compound of formula (IV) may be reacted with phosphorous tribromide in a solvent, e.g. dichloromethane, at reduced temperatures, e.g. less than -10°C.

Suitable reaction conditions for the reaction of a compound of formula (V) with a compound R<sup>x</sup>-L to give a compound of formula (IV) are known to those skilled in the art and include the use of a solvent e.g. a C<sub>1-4</sub>alcohol such as methanol or ethanol in the presence of a base, e.g. sodium hydroxide.

Accordingly the present invention also provides a process for the preparation of a compound of formula (I) or a derivative thereof:

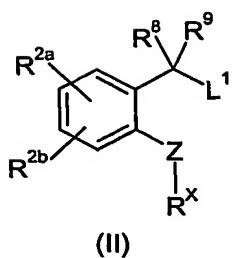


wherein:

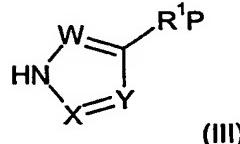
- 5    W represents N or CR<sup>10</sup> wherein R<sup>10</sup> represents hydrogen, halogen, optionally substituted alkyl, optionally substituted aryl, or optionally substituted heterocyclyl;
- X represents N or CR<sup>11</sup> wherein R<sup>11</sup> represents hydrogen, halogen, optionally substituted alkyl, optionally substituted aryl, or optionally substituted heterocyclyl;
- Y represents N or CR<sup>12</sup> wherein R<sup>12</sup> represents hydrogen, halogen, CH<sub>3</sub> or CF<sub>3</sub>;
- 10   Z represents O, S, SO or SO<sub>2</sub>;  
      R<sup>1</sup> represents CO<sub>2</sub>R<sup>4</sup>, CONR<sup>5</sup>R<sup>6</sup>, CH<sub>2</sub>CO<sub>2</sub>H, optionally substituted SO<sub>2</sub>alkyl, SO<sub>2</sub>NR<sup>5</sup>R<sup>8</sup>, NR<sup>5</sup>CONR<sup>5</sup>R<sup>6</sup>, 2H-tetrazol-5-yl-methyl or optionally substituted heterocyclyl;
- R<sup>2a</sup> and R<sup>2b</sup> independently represents hydrogen, halo, optionally substituted alkyl, optionally substituted alkoxy, CN, SO<sub>2</sub>alkyl, SR<sup>5</sup>, NO<sub>2</sub>, optionally substituted aryl, CONR<sup>5</sup>R<sup>8</sup> or optionally substituted heteroaryl;
- 15   R<sup>x</sup> represents optionally substituted alkyl wherein 1 or 2 of the non-terminal carbon atoms are optionally replaced by a group independently selected from NR<sup>4</sup>, O and SO<sub>n</sub>, wherein n is 0, 1 or 2; or R<sup>x</sup> represents optionally substituted CQ<sup>a</sup>Q<sup>b</sup>-heterocyclyl, optionally substituted CQ<sup>a</sup>Q<sup>b</sup>-bicyclic heterocyclyl or optionally substituted CQ<sup>a</sup>Q<sup>b</sup>-aryl;
- 20   R<sup>4</sup> represents hydrogen or an optionally substituted alkyl;  
      R<sup>5</sup> represents hydrogen or an optionally substituted alkyl;  
      R<sup>6</sup> represents hydrogen or optionally substituted alkyl, optionally substituted heteroaryl, optionally substituted SO<sub>2</sub>aryl, optionally substituted SO<sub>2</sub>alkyl, optionally substituted SO<sub>2</sub>heteroaryl, CN, optionally substituted CQ<sup>a</sup>Q<sup>b</sup>aryl, optionally substituted CQ<sup>a</sup>Q<sup>b</sup>heteroaryl or COR<sup>7</sup>;
- 25   R<sup>7</sup> represents hydrogen, optionally substituted alkyl, optionally substituted heteroaryl or optionally substituted aryl;  
      R<sup>8</sup> and R<sup>9</sup> are independently selected from hydrogen, fluorine or alkyl, or R<sup>8</sup> and R<sup>9</sup> together with the carbon to which they are attached form a cycloalkyl ring, optionally containing up to one heteroatom selected from O, S, NH or N-alkyl;
- 30   wherein Q<sup>a</sup> and Q<sup>b</sup> are each independently selected from hydrogen, CH<sub>3</sub> and fluorine;

comprising:

reacting a compound of formula (II):



wherein  $L^1$  is a leaving group and  $Z$ ,  $R^8$ ,  $R^9$ ,  $R^{2a}$ ,  $R^{2b}$ , and  $R^X$  are as defined above for a compound of formula (I);  
with a compound of formula (III):



5

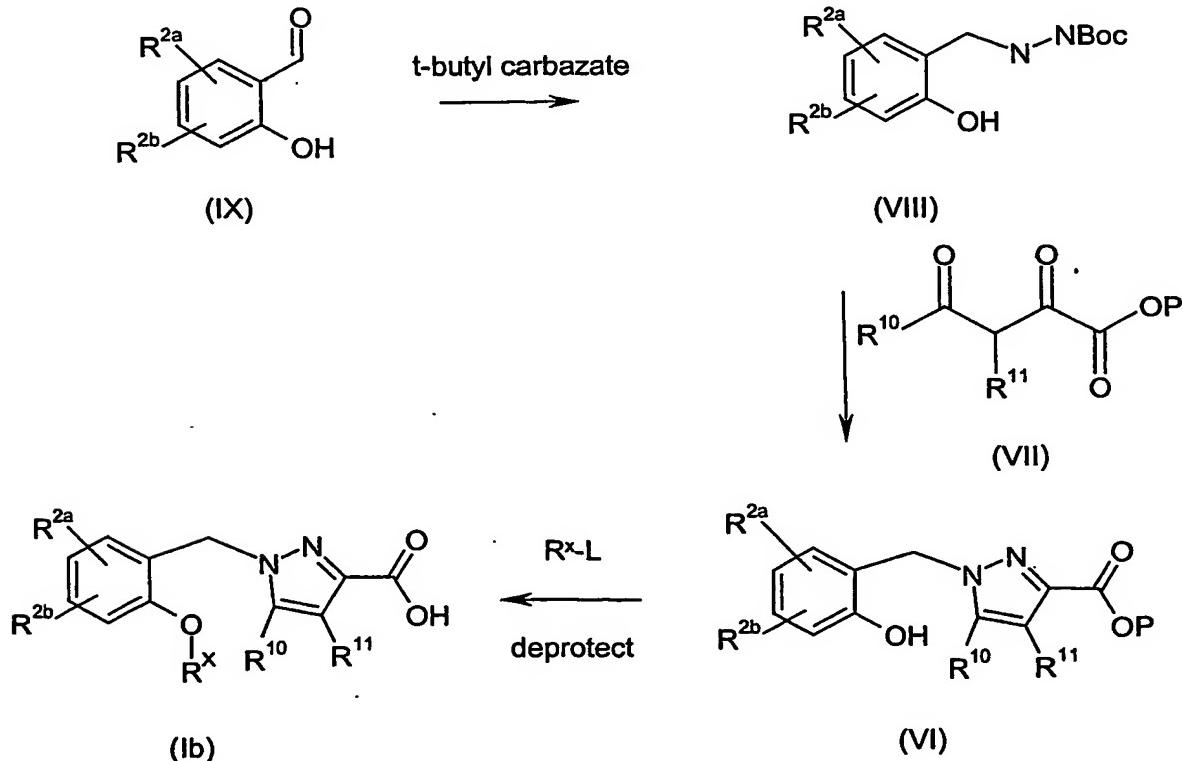
wherein  $W$ ,  $X$ ,  $Y$ , and  $R^1$  are as defined above for a compound of formula (I) and  $P$  is an optional protecting group;

and where required, and in any order:

- interconverting one substituent to another substituent; and/or
- 10 if necessary removing the optional protecting group; and/or
- forming a derivative thereof.

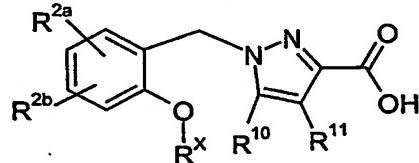
Compounds of formula (I) wherein  $Z$  is O,  $W$  is N,  $X$  is  $CR^{10}$ ,  $Y$  is  $CR^{11}$ , and  $R^1$  is COOH may be prepared by the general route below:

15



wherein L is a leaving group for example halo, e.g. bromo; P is a protecting group for example C<sub>1-4</sub> alkyl e.g. methyl or ethyl; and R<sup>2a</sup>, R<sup>2b</sup>, R<sup>10</sup>, R<sup>11</sup> and R<sup>x</sup> are as defined for compounds of formula (Ia).

- 5 Accordingly the present invention also provides a process for the preparation of a compound of formula (Ib) or a derivative thereof:



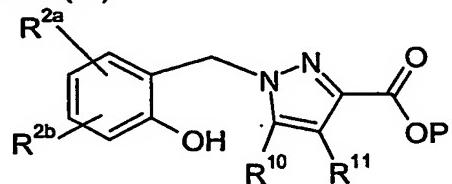
(Ib)

wherein:

- R<sup>2a</sup> and R<sup>2b</sup> independently represents hydrogen, halo, optionally substituted alkyl, 10 optionally substituted alkoxy, CN, SO<sub>2</sub>alkyl, SR<sup>5</sup>, NO<sub>2</sub>, optionally substituted aryl, CONR<sup>5</sup>R<sup>6</sup> or optionally substituted heteroaryl;
- R<sup>x</sup> represents optionally substituted alkyl wherein 1 or 2 of the non-terminal carbon atoms are optionally replaced by a group independently selected from NR<sup>4</sup>, O and SO<sub>n</sub>, wherein n is 0, 1 or 2; or R<sup>x</sup> may be optionally substituted CQ<sup>a</sup>Q<sup>b</sup>-heterocyclyl, optionally substituted 15 CQ<sup>a</sup>Q<sup>b</sup>-bicyclic heterocyclyl or optionally substituted CQ<sup>a</sup>Q<sup>b</sup>-aryl;
- R<sup>4</sup> represents hydrogen or an optionally substituted alkyl;
- R<sup>5</sup> represents hydrogen or an optionally substituted alkyl;
- R<sup>6</sup> represents hydrogen or optionally substituted alkyl, optionally substituted heteroaryl, 20 optionally substituted SO<sub>2</sub>aryl, optionally substituted SO<sub>2</sub>alkyl, optionally substituted SO<sub>2</sub>heteroaryl, CN, optionally substituted CQ<sup>a</sup>Q<sup>b</sup>aryl, optionally substituted CQ<sup>a</sup>Q<sup>b</sup>-heteroaryl or COR<sup>7</sup>;
- R<sup>7</sup> represents hydrogen, optionally substituted alkyl, optionally substituted heteroaryl or 25 optionally substituted aryl;
- R<sup>10</sup> represents hydrogen, halogen, optionally substituted alkyl, optionally substituted aryl, or optionally substituted heterocyclyl; and
- R<sup>11</sup> represents hydrogen, halogen, optionally substituted alkyl, optionally substituted aryl, or optionally substituted heterocyclyl;
- wherein Q<sup>a</sup> and Q<sup>b</sup> are each independently selected from hydrogen, CH<sub>3</sub> and fluorine;

- 30 comprising:

reacting a compound of formula (VI):



(VI)

wherein R<sup>2a</sup>, R<sup>2b</sup>, R<sup>10</sup> and R<sup>11</sup> are as defined above for a compound of formula (Ib) and P is a protecting group;

with R<sup>x</sup> - L wherein R<sup>x</sup> is as defined for compounds of formula (I) and L is a leaving group; and where required, and in any order:

- 5 interconverting one substituent to another substituent; and/or removing the protecting group; and/or forming a derivative thereof.

When one or both of R<sup>10</sup> and R<sup>11</sup> is/are halogen, preferably the halogen group is

- 10 introduced after the ring forming reaction of a compound of formula (VII) and (VIII).

Suitable fluorination conditions are described in e.g. K. Makino et al, *J. Fluor. Chem.*, 1988, 39, 435-440. Halogenation conditions are also reviewed in e.g. *Comprehensive heterocyclic chemistry. The structure, reactions, synthesis and uses of heterocyclic compounds*, A.R. Katritzky and C.W. Rees (Eds), vols 1-8, Pergamon Press, Oxford, 1984; *Comprehensive organic chemistry II. A review of the literature 1982-1995*, A.R.

- 15 Katritzky, C.W. Rees, and E.F.V. Scriven (eds), vols 1-11, Pergamon Press, Oxford, 1996, and *Heterocyclic Chemistry*, 4th Edition, J.A. Joule and K. Mills, Blackwell Science, 2000.

Suitable reaction conditions for the reaction of a compound of formula (VI) with a

- 20 compound R<sup>x</sup>-L are known to those skilled in the art and include the use of a solvent e.g. a C<sub>1-4</sub>alcohol such as methanol or ethanol in the presence of a base, e.g. sodium hydroxide. Suitable conditions for the deprotection of an ester to give the corresponding carboxylic acid are known to those skilled in the art.

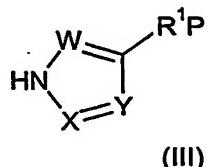
- 25 Suitable reaction conditions for the reaction of a compound of formula (VII) with a compound of formula (VIII) to give a pyrazole of formula (VI) will be apparent to the skilled person and include treatment with trifluoroacetic acid in a solvent, e.g. dichloromethane, at room temperature to remove the protecting group on the compound of formula (VIII) followed by cyclisation with (VII) in acidic conditions.

- 30 Suitable reaction conditions for the conversion of a salicylaldehyde of formula (IX) to a compound of formula (VIII) include reacting the salicylaldehyde with *tert*-butyl carbazate in the presence of acetic acid and sodium triacetoxyborohydride in a solvent such as dichloromethane.

- 35 Compounds R<sup>x</sup>-L and compounds of formula (III), (V), (VII), (IX) and *t*-butyl carbazate are commercially available, or may be readily prepared from commercially available intermediates by methods known to those skilled in the art.

Compounds of formula  $R^x-L$  wherein L is as defined above and  $R^x$  is as defined for compounds of formula (I) are commercially available, or may be readily prepared by known transformations of commercially available compounds.

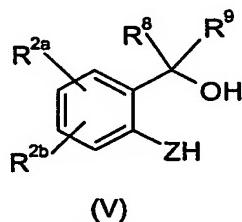
5 Compounds of formula (III):



wherein W, X, Y and  $R^1$  are as defined for compounds of formula (I) and P is an optional protecting group are commercially available, or may be prepared by conventional processes for the preparation of pyrroles, pyrazoles, triazoles and tetrazoles. The

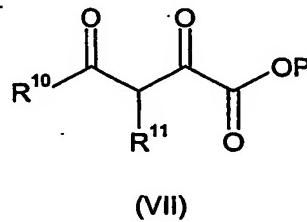
- 10 preparation of pyrroles, pyrazoles, tetrazoles and triazoles is reviewed in e.g. *Comprehensive heterocyclic chemistry. The structure, reactions, synthesis and uses of heterocyclic compounds*, A.R. Katritzky and C.W. Rees (Eds), vols 1-8, Pergamon Press, Oxford, 1984; *Comprehensive organic chemistry II. A review of the literature 1982-1995*, A.R. Katritzky, C.W. Rees, and E.F.V. Scriven (eds), vols 1-11, Pergamon Press, Oxford, 15 1996, and *Heterocyclic Chemistry*, 4th Edition, J.A. Joule and K. Mills, Blackwell Science, 2000.

Compounds of formula (V):



- 20 wherein  $R^{2a}$ ,  $R^{2b}$ ,  $R^8$ , and  $R^9$  are as defined for compounds of formula (I) are commercially available, or may be prepared from commercially available intermediates by conventional methods. For example, processes for the preparation of 2-(hydroxymethyl)phenols are described in W.A. Sheppard, *J. Org. Chem.*, 1968, 33, 3297-3306.

25 Intermediates of formula (VII):

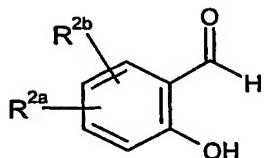


wherein  $R^{10}$  and  $R^{11}$  are as defined for compounds of formula (Ia), and P is  $C_{1-4}$  alkyl e.g. methyl or ethyl, are commercially available or may be prepared from commercial

intermediates by known processes for the preparation of 1,3-diketones e.g. J. Royals, *J. Amer. Chem. Soc.* 1945, 67, 1508.

Intermediates of formula (IX):

5



wherein  $R^{2a}$  and  $R^{2b}$  are as defined for compounds of formula (I) are commercially available, or may readily be prepared by methods known to those skilled in the art, for example from suitable commercially available starting materials using methods as described in the examples. The preparation of aldehydes is reviewed in *The Chemistry of the Carbonyl Group*, S. Patai (Ed), Interscience, New York, 1966, and references cited therein.

Certain substituents in any of the reaction intermediates and compounds of formula (I)

15 may be converted to other substituents by conventional methods known to those skilled in the art. Examples of such transformations include the reduction of a nitro group to give an amino group; alkylation and amidation of amino groups; hydrolysis of esters, alkylation of hydroxy and amino groups; and amidation and esterification of carboxylic acids. Such transformations are well known to those skilled in the art and are described in for example, 20 Richard Larock, *Comprehensive Organic Transformations*, 2nd edition, Wiley-VCH, ISBN 0-471-19031-4. Fluorination of pyrazoles is described in e.g. K. Makino *et al*, *J. Fluor. Chem.*, 1988, 39, 435-440. When  $R^{10}$  is alkyl, the  $R^{10}$  group may be incorporated via C-metallation and alkylation as described in, for example, *Heterocyclic Chemistry*, 4th Edition, J.A. Joule and K. Mills, Blackwell Science, 2000.

25

For example, when  $R^x$  is p-methoxybenzyl, cleavage of the ether to give the phenol is carried out using, for example, using acid e.g. HCl/dioxane or using sodium methanethiolate. Conversion to another  $R^x$  group, for example a substituted benzyl group, may be effected by reaction of the phenol with a suitable substituted benzyl bromide. The 30 skilled person will appreciate that conversion of the protecting group P to another protecting group P may also occur under the reaction conditions used. When  $R^x$  is benzyl, cleavage of the ether to give the phenol may be carried out by hydrogenation according to known methods e.g.  $H_2$ -Pd/C or  $NH_4CO_2H$ -Pd/C. The resulting phenol can then be converted to another group  $R^x$  as described above.

35

It will be appreciated by those skilled in the art that it may be necessary to protect certain reactive substituents during some of the above procedures. The skilled person will recognise when a protecting group is required. Standard protection and deprotection techniques, such as those described in Greene T.W. 'Protective groups in organic

synthesis', New York, Wiley (1981), can be used. For example, carboxylic acid groups can be protected as esters. Deprotection of such groups is achieved using conventional procedures known in the art. It will be appreciated that protecting groups may be interconverted by conventional means.

5

It is to be understood that the present invention encompasses all isomers of formula (I) and their pharmaceutically acceptable derivatives, including all geometric, tautomeric and optical forms, and mixtures thereof (e.g. racemic mixtures). Where additional chiral centres are present in compounds of formula (I), the present invention includes within its scope all possible diastereoisomers, including mixtures thereof. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses.

15

The compounds of the invention bind to the EP<sub>1</sub> receptor and they are therefore considered to be useful in treating conditions mediated by the action of PGE<sub>2</sub> at EP<sub>1</sub> receptors.

20

Conditions mediated by the action of PGE<sub>2</sub> at EP<sub>1</sub> receptors include pain; fever; inflammation; immunological diseases; abnormal platelet function diseases; impotence or erectile dysfunction; bone disease; hemodynamic side effects of non-steroidal anti-inflammatory drugs; cardiovascular diseases; neurodegenerative diseases and neurodegeneration; neurodegeneration following trauma; tinnitus; dependence on a dependence-inducing agent; complications of Type I diabetes; and kidney dysfunction.

25

The compounds of formula (I) and pharmaceutically acceptable derivatives thereof are considered to be useful as analgesics. They are therefore considered useful in the treatment or prevention of pain.

30

The compounds of formula (I) and pharmaceutically acceptable derivatives thereof are considered useful as analgesics to treat acute pain, chronic pain, neuropatic pain, inflammatory pain, visceral pain, pain associated with cancer and fibromyalgia, pain associated with migraine, tension headache and cluster headaches, and pain associated with functional bowel disorders, non-cardiac chest pain and non-ulcer dispepsia.

35

The compounds of formula (I) and pharmaceutically acceptable derivatives thereof are considered useful in the treatment of chronic articular pain (e.g. rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis and juvenile arthritis) including the property of disease modification and joint structure preservation; musculoskeletal pain; lower back and neck pain; sprains and strains; neuropathic pain; sympathetically maintained pain; myositis; pain associated with cancer and fibromyalgia; pain associated with migraine; pain associated with influenza or other viral infections, such as the common cold; rheumatic fever; pain associated with functional bowel disorders such as non-ulcer

dyspepsia, non-cardiac chest pain and irritable bowel syndrome; pain associated with myocardial ischemia; post operative pain; headache; toothache; and dysmenorrhea.

The compounds of the invention are considered to be particularly useful in the treatment of neuropathic pain. Neuropathic pain syndromes can develop following neuronal injury and the resulting pain may persist for months or years, even after the original injury has healed. Neuronal injury may occur in the peripheral nerves, dorsal roots, spinal cord or certain regions in the brain. Neuropathic pain syndromes are traditionally classified according to the disease or event that precipitated them. Neuropathic pain syndromes include: diabetic neuropathy; sciatica; non-specific lower back pain; multiple sclerosis pain; fibromyalgia; HIV-related neuropathy; post-herpetic neuralgia; trigeminal neuralgia; and pain resulting from physical trauma, amputation, cancer, toxins or chronic inflammatory conditions. These conditions are difficult to treat and although several drugs are known to have limited efficacy, complete pain control is rarely achieved. The symptoms of neuropathic pain are incredibly heterogeneous and are often described as spontaneous shooting and lancinating pain, or ongoing, burning pain. In addition, there is pain associated with normally non-painful sensations such as "pins and needles" (paraesthesiae and dysesthesias), increased sensitivity to touch (hyperesthesia), painful sensation following innocuous stimulation (dynamic, static or thermal allodynia), increased sensitivity to noxious stimuli (thermal, cold, mechanical hyperalgesia), continuing pain sensation after removal of the stimulation (hyperpathia) or an absence of or deficit in selective sensory pathways (hypoalgesia).

The compounds of formula (I) and pharmaceutically acceptable derivatives thereof are also considered useful in the treatment of fever.

The compounds of formula (I) and pharmaceutically acceptable derivatives thereof are also considered useful in the treatment of inflammation, for example in the treatment of skin conditions (e.g. sunburn, burns, eczema, dermatitis, psoriasis); ophthalmic diseases such as glaucoma, retinitis, retinopathies, uveitis and of acute injury to the eye tissue (e.g. conjunctivitis); lung disorders (e.g. asthma, bronchitis, emphysema, allergic rhinitis, respiratory distress syndrome, pigeon fancier's disease, farmer's lung, chronic obstructive pulmonary disease, (COPD); gastrointestinal tract disorders (e.g. aphthous ulcer, Crohn's disease, atopic gastritis, gastritis varioliforme, ulcerative colitis, coeliac disease, regional ileitis, irritable bowel syndrome, inflammatory bowel disease, gastrointestinal reflux disease); organ transplantation; other conditions with an inflammatory component such as vascular disease, migraine, periarthritis nodosa, thyroiditis, aplastic anaemia, Hodgkin's disease, sclerodema, myasthenia gravis, multiple sclerosis, sarcoidosis, nephrotic syndrome, Bechet's syndrome, gingivitis, myocardial ischemia, pyrexia, systemic lupus erythematosus, polymyositis, tendinitis, bursitis, and Sjogren's syndrome.

The compounds of formula (I) and pharmaceutically acceptable derivatives thereof are also considered useful in the treatment of immunological diseases such as autoimmune

diseases, immunological deficiency diseases or organ transplantation. The compounds of formula (I) are also effective in increasing the latency of HIV infection.

5 The compounds of formula (I) and pharmaceutically acceptable derivatives thereof are also considered useful in the treatment of diseases relating to abnormal platelet function (e.g. occlusive vascular diseases).

10 The compounds of formula (I) and pharmaceutically acceptable derivatives thereof are also considered useful for the preparation of a drug with diuretic action.

15 The compounds of formula (I) and pharmaceutically acceptable derivatives thereof are also considered useful in the treatment of impotence or erectile dysfunction.

20 The compounds of formula (I) and pharmaceutically acceptable derivatives thereof are also considered useful in the treatment of bone disease characterised by abnormal bone metabolism or resorption such as osteoporosis (especially postmenopausal osteoporosis), hypercalcemia, hyperparathyroidism, Paget's bone diseases, osteolysis, hypercalcemia of malignancy with or without bone metastases, rheumatoid arthritis, periodontitis, osteoarthritis, ostealgia, osteopenia, cancer cachexia, calculosis, lithiasis (especially urolithiasis), solid carcinoma, gout and ankylosing spondylitis, tendinitis and bursitis.

25 The compounds of formula (I) and pharmaceutically acceptable derivatives thereof are also considered useful for attenuating the hemodynamic side effects of non-steroidal anti-inflammatory drugs (NSAID's) and cyclooxygenase-2 (COX-2) inhibitors.

30 The compounds of formula (I) and pharmaceutically acceptable derivatives thereof are also considered useful in the treatment of cardiovascular diseases such as hypertension or myocardial ischemia; functional or organic venous insufficiency; varicose therapy; haemorrhoids; and shock states associated with a marked drop in arterial pressure (e.g. septic shock).

35 The compounds of formula (I) and pharmaceutically acceptable derivatives thereof are also considered useful in the treatment of neurodegenerative diseases and neurodegeneration such as dementia, particularly degenerative dementia (including senile dementia, Alzheimer's disease, Pick's disease, Huntingdon's chorea, Parkinson's disease and Creutzfeldt-Jakob disease, ALS, motor neuron disease); vascular dementia (including multi-infarct dementia); as well as dementia associated with intracranial space occupying lesions; trauma; infections and related conditions (including HIV infection); metabolism; toxins; anoxia and vitamin deficiency; and mild cognitive impairment associated with ageing, particularly Age Associated Memory Impairment.

40 The compounds of formula (I) and pharmaceutically acceptable derivatives thereof are also considered useful in the treatment of neuroprotection and in the treatment of

neurodegeneration following trauma such as stroke, cardiac arrest, pulmonary bypass, traumatic brain injury, spinal cord injury or the like.

5 The compounds of formula (I) and pharmaceutically acceptable derivatives thereof are also considered useful in the treatment of tinnitus.

The compounds of formula (I) and pharmaceutically acceptable derivatives thereof are also considered useful in preventing or reducing dependence on, or preventing or reducing tolerance or reverse tolerance to, a dependence - inducing agent. Examples of  
10 dependence inducing agents include opioids (e.g. morphine), CNS depressants (e.g. ethanol), psychostimulants (e.g. cocaine) and nicotine.

The compounds of formula (I) and pharmaceutically acceptable derivatives thereof are also considered useful in the treatment of complications of Type 1 diabetes (e.g. diabetic  
15 microangiopathy, diabetic retinopathy, diabetic nephropathy, macular degeneration, glaucoma), nephrotic syndrome, aplastic anaemia, uveitis, Kawasaki disease and sarcoidosis.

20 The compounds of formula (I) and pharmaceutically acceptable derivatives thereof are also considered useful in the treatment of kidney dysfunction (nephritis, particularly mesangial proliferative glomerulonephritis, nephritic syndrome), liver dysfunction (hepatitis, cirrhosis), gastrointestinal dysfunction (diarrhoea) and colon cancer.

25 The compounds of formula (I) and pharmaceutically acceptable derivatives thereof are also useful in the treatment of overactive bladder and urge incontinence.

It is to be understood that reference to treatment includes both treatment of established symptoms and prophylactic treatment, unless explicitly stated otherwise.

30 According to a further aspect of the invention, we provide a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use in human or veterinary medicine.

According to another aspect of the invention, we provide a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use in the treatment of a condition which  
35 is mediated by the action of PGE<sub>2</sub> at EP<sub>1</sub> receptors.

According to a further aspect of the invention, we provide a method of treating a human or animal subject suffering from a condition which is mediated by the action of PGE<sub>2</sub> at EP<sub>1</sub> receptors which comprises administering to said subject an effective amount of a  
40 compound of formula (I) or a pharmaceutically acceptable derivative thereof.

According to a further aspect of the invention we provide a method of treating a human or animal subject suffering from a pain, inflammatory, immunological, bone,

neurodegenerative or renal disorder, which method comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

- 5 According to a yet further aspect of the invention we provide a method of treating a human or animal subject suffering from inflammatory pain, neuropathic pain or visceral pain which method comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.
- 10 According to another aspect of the invention, we provide the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment of a condition which is mediated by the action of PGE<sub>2</sub> at EP<sub>1</sub> receptors.
- 15 According to another aspect of the invention we provide the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment or prevention of a condition such as a pain, inflammatory, immunological, bone, neurodegenerative or renal disorder.
- 20 According to another aspect of the invention we provide the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment or prevention of a condition such as inflammatory pain, neuropathic pain or visceral pain.
- 25 The compounds of formula (I) and their pharmaceutically acceptable derivatives are conveniently administered in the form of pharmaceutical compositions. Such compositions may conveniently be presented for use in conventional manner in admixture with one or more physiologically acceptable carriers or excipients.
- 30 Thus, in another aspect of the invention, we provide a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof adapted for use in human or veterinary medicine.
- 35 The compounds of formula (I) and their pharmaceutically acceptable derivatives may be formulated for administration in any suitable manner. They may, for example, be formulated for topical administration or administration by inhalation or, more preferably, for oral, transdermal or parenteral administration. The pharmaceutical composition may be in a form such that it can effect controlled release of the compounds of formula (I) and their pharmaceutically acceptable derivatives.

For oral administration, the pharmaceutical composition may take the form of, for example, tablets (including sub-lingual tablets), capsules, powders, solutions, syrups or suspensions prepared by conventional means with acceptable excipients.

- 5 For transdermal administration, the pharmaceutical composition may be given in the form of a transdermal patch, such as a transdermal iontophoretic patch.

For parenteral administration, the pharmaceutical composition may be given as an injection or a continuous infusion (e.g. intravenously, intravascularly or subcutaneously).

- 10 The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. For administration by injection these may take the form of a unit dose presentation or as a multidose presentation preferably with an added preservative. Alternatively for parenteral administration the active ingredient may be in powder form for

- 15 reconstitution with a suitable vehicle.

The compounds of the invention may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the

- 20 compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

- 25 The EP<sub>1</sub> receptor compounds for use in the instant invention may be used in combination with other therapeutic agents, for example COX-2 inhibitors, such as celecoxib, deracoxib, rofecoxib, valdecoxib, parecoxib or COX-189; 5-lipoxygenase inhibitors; NSAID's, such as diclofenac, indomethacin, nabumetone or ibuprofen; leukotriene receptor antagonists; DMARD's such as methotrexate; adenosine A1 receptor agonists; sodium channel blockers, such as lamotrigine; NMDA receptor modulators, such as glycine receptor
- 30 antagonists; gabapentin and related compounds; tricyclic antidepressants such as amitriptyline; neurone stabilising antiepileptic drugs; mono-aminergic uptake inhibitors such as venlafaxine; opioid analgesics; local anaesthetics; 5HT<sub>1</sub> agonists, such as triptans, for example sumatriptan, naratriptan, zolmitriptan, eletriptan, frovatriptan, almotriptan or rizatriptan; nicotinic acetyl choline (nACh) receptor modulators; glutamate receptor
- 35 modulators, for example modulators of the NR2B ssubtype; EP<sub>4</sub> receptor ligands; EP<sub>2</sub> receptor ligands; EP<sub>3</sub> receptor ligands; EP<sub>4</sub> antagonists; EP<sub>2</sub> antagonists and EP<sub>3</sub> antagonists; cannabinoid receptor ligands; bradykinin receptor ligands and vanilloid receptor ligand. When the compounds are used in combination with other therapeutic agents, the compounds may be administered either sequentially or simultaneously by any
- 40 convenient route.

Additional COX-2 inhibitors are disclosed in US Patent Nos. 5,474,995 US5,633,272; US5,466,823, US6,310,099 and US6,291,523; and in WO 96/25405, WO 97/38986, WO 98/03484, WO 97/14691, WO99/12930, WO00/26216, WO00/52008, WO00/38311, WO01/58881 and WO02/18374.

5

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof together with a further therapeutic agent or agents.

10 In addition to activity at the EP<sub>1</sub> receptor, the compounds of the present invention and pharmaceutically acceptable derivatives thereof exhibit antagonism of the TP receptor and are therefore indicated to be useful in treating conditions mediated by the action of thromboxane at the TP receptor.

15 In view of their antagonism of the TP receptor, the compounds of the invention and pharmaceutically acceptable derivatives thereof are indicated to be useful in the treatment of renal disorders, asthma, or gastric lesions.

20 Certain compounds of the invention are equipotent antagonists of the EP<sub>1</sub> and TP receptors.

The present invention therefore also provides a compound which is an equipotent antagonist of the TP receptor and the EP<sub>1</sub> receptor.

25 According to another aspect of the invention, we provide a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use in the treatment of a condition which is mediated by the action of thromboxane at the TP receptor.

30 According to a further aspect of the invention, we provide a method of treating a human or animal subject suffering from a condition which is mediated by the action of thromboxane at the TP receptor which comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

35 According to a yet further aspect of the invention we provide a method of treating a human or animal subject suffering from a renal disorder, asthma, or gastric lesions, which method comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

40 According to another aspect of the invention, we provide the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment of a condition which is mediated by the action of thromboxane at the TP receptor.

According to another aspect of the invention we provide the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment or prevention of a condition such as a renal disorder, 5 asthma, or gastric lesions.

In certain situations it is envisaged that the administration of a compound exhibiting antagonism of TP receptors in combination with a compound exhibiting antagonism of EP<sub>1</sub> receptors may be advantageously beneficial.

- 10 The present invention therefore also provides a composition comprising an EP<sub>1</sub> antagonist or a pharmaceutically acceptable derivative thereof and a TP antagonist or a pharmaceutically acceptable derivative thereof.
- 15 According to a further aspect, we provide a combination comprising an EP<sub>1</sub> antagonist or a pharmaceutically acceptable derivative thereof and a TP antagonist or a pharmaceutically acceptable derivative thereof for use in the treatment of a condition which is mediated by the action of PGE<sub>2</sub> at EP<sub>1</sub> receptors.
- 20 The present invention also provides a combination comprising an EP<sub>1</sub> antagonist or a pharmaceutically acceptable derivative thereof and a TP antagonist or a pharmaceutically acceptable derivative thereof for use in the treatment of pain, or inflammatory, immunological, bone, neurodegenerative or renal disorders.
- 25 The present invention further provides a combination comprising an EP<sub>1</sub> antagonist or a pharmaceutically acceptable derivative thereof and a TP antagonist or a pharmaceutically acceptable derivative thereof for use in the treatment of inflammatory pain, neuropathic pain or visceral pain.
- 30 According to a further aspect of the invention we provide a method of treating a human or animal subject suffering from a pain, or an inflammatory, immunological, bone, neurodegenerative or renal disorder, which method comprises administering to said subject a combination comprising an effective amount of an EP<sub>1</sub> antagonist or a pharmaceutically acceptable derivative thereof and an effective amount of a TP antagonist or a pharmaceutically acceptable derivative thereof.
- 35 According to a yet further aspect of the invention we provide a method of treating a human or animal subject suffering from inflammatory pain, neuropathic pain or visceral pain which method comprises administering to said subject a combination comprising an effective amount of an EP<sub>1</sub> antagonist or a pharmaceutically acceptable derivative thereof and an effective amount of a TP antagonist or a pharmaceutically acceptable derivative thereof.

According to another aspect of the invention, we provide the use an EP<sub>1</sub> antagonist or a pharmaceutically acceptable derivative thereof in combination with a TP antagonist or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment of a condition which is mediated by the action of PGE<sub>2</sub> at EP<sub>1</sub> receptors.

5

According to another aspect of the invention we provide the use an EP<sub>1</sub> antagonist or a pharmaceutically acceptable derivative thereof in combination with a TP antagonist or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment of or prevention of a condition such as a pain, or an inflammatory,

10

immunological, bone, neurodegenerative or renal disorder.

15

According to another aspect of the invention we provide the use of use an EP<sub>1</sub> antagonist or a pharmaceutically acceptable derivative thereof in combination with a TP antagonist or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment or prevention of a condition such as inflammatory pain, neuropathic pain or visceral pain.

20

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

25

When a compound of formula (I) or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same disease state the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

30

A proposed daily dosage of compounds of formula (I) or their pharmaceutically acceptable derivatives for the treatment of man is from 0.01 to 30 mg/kg body weight per day and more particularly 0.1 to 10 mg/kg body weight per day, calculated as the free base, which may be administered as a single or divided dose, for example one to four times per day. The dose range for adult human beings is generally from 8 to 2000 mg/day, such as from 35

35

20 to 1000 mg/day, preferably 35 to 200 mg/day, calculated as the free base.

40

The precise amount of the compounds of formula (I) administered to a host, particularly a human patient, will be the responsibility of the attendant physician. However, the dose employed will depend on a number of factors including the age and sex of the patient, the precise condition being treated and its severity, and the route of administration.

No unacceptable toxicological effects are expected with compounds of the invention when administered in accordance with the invention.

5 All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

10 The following non-limiting Examples illustrate the preparation of pharmacologically active compounds of the invention.

**EXAMPLES****Abbreviations**

- 5 Dimethylsulfoxide (DMSO); acetonitrile (MeCN); methanol (MeOH); Solid phase extraction (SPE); liquid chromatography/mass spectrometry (LCMS); NMR (nuclear magnetic resonance);

**LCMS**

10

- Column: 3.3cm x 4.6mm ID, 3um ABZ+PLUS
- Flow Rate: 3ml/min
- Injection Volume: 5 $\mu$ l
- Temp: RT
- UV Detection Range: 215 to 330nm
- 

15

Solvents: A: 0.1% Formic Acid + 10mMolar Ammonium Acetate.  
 B: 95% Acetonitrile + 0.05% Formic Acid

Gradient:	Time	A%	B%
	0.00	100	0
	0.70	100	0
	4.20	0	100
	5.30	0	100
	5.50	100	0

**Mass Directed Autopreparation**

20

Hardware:

- Waters 600 gradient pump  
 Waters 2767 inject/collector  
 Waters Reagent Manager  
 Micromass ZMD mass spectrometer  
 Gilson Aspec - waste collector  
 Gilson 115 post-fraction UV detector

Software :

Micromass Masslynx version 4.0

30

Column

The column used is typically a Supelco LCABZ++ column whose dimensions are 20mm internal diameter by 100mm in length. The stationary phase particle size is 5 $\mu$ m.

Solvents:

A.: Aqueous solvent = Water + 0.1% Formic Acid

35

B: Organic solvent = MeCN: Water 95:5 +0.05% Formic Acid

Make up solvent = MeOH: Water 80:20 +50mMol Ammonium Acetate  
 Needle rinse solvent = MeOH: Water: DMSO 80:10:10

The method used depends on the analytical retention time of the compound of interest.

- 5      15-minute runtime, which comprises a 10-minute gradient followed by a 5-minute column flush and re-equilibration step.

MDP 1.5-2.2 = 0-30% B

MDP 2.0-2.8 = 5-30% B

MDP 2.5-3.0 = 15-55% B

- 10     MDP 2.8-4.0 = 30-80% B

MDP 3.8-5.5 = 50-90% B

Flow rate:

flow rate 20ml/min.

15

**General Method 1**

Preparation of 4-bromo-2-(bromomethyl)phenyl phenylmethyl ether (Intermediate A)



20

a) {5-bromo-2-[(phenylmethyl)oxy]phenyl}methanol

4-bromo-2-(hydroxymethyl)phenol (10.15g, 50mmol) was dissolved in ethanol (100ml) and 2M sodium hydroxide (27.5ml, 55mmol). The resulting solution was stirred for 10 minutes. A solution of [benzyl bromide] (5.95ml, 50mmol) in ethanol (100ml) was added slowly and

- 25     the resulting solution was stirred overnight at room temperature. The reaction mixture was concentrated *in vacuo*, the solution obtained diluted with water and extracted with dichloromethane. The combined organic layers were washed sequentially with a saturated solution of NaHCO<sub>3</sub> and water, dried (Na<sub>2</sub>SO<sub>4</sub>) filtered and evaporated to dryness. The residue was purified by flash chromatography using dichloromethane to yield the title compound as a colourless oil (13.8g, 94%).

<sup>1</sup>H NMR δ: 2.19 (1H, t), 4.71 (2H, d, J = 6.3Hz), 5.10 (2H, s), 6.82 (1H, d, J = 8.6Hz), 7.34-7.47 (7H, m).

b) 4-bromo-2-(bromomethyl)phenyl phenylmethyl ether (Intermediate A)

- 35     A solution of {5-bromo-2-[(phenylmethyl)oxy]phenyl}methanol (5.41g, 18.44mmol) in dichloromethane (30ml) was stirred under nitrogen and cooled to -10°C (ice/acetone). A solution of phosphorous tribromide (4.99g, 1.75ml, 18.44mmol) in dichloromethane (15ml) was added slowly at -10°C and the mixture warmed to -7°C and stirred for 15 mins. The

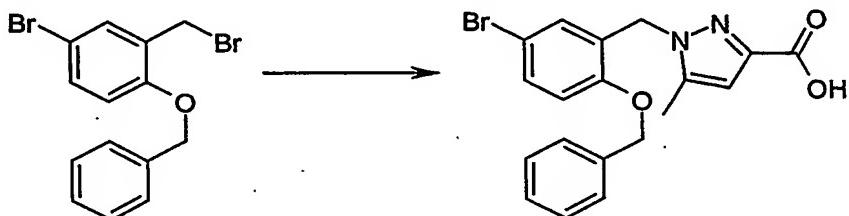
reaction was then allowed to warm to room temperature and was stirred overnight under nitrogen. The reaction mixture was cooled (ice/water bath) and a saturated sodium hydrogen carbonate solution (15.5ml) was then added slowly and the mixture diluted with dichloromethane and water. The organic phase was separated, washed with water then dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated to dryness. The residue was purified by flash chromatography with diethyl ether to yield the title compound as a white solid (5.53g, 84%).

$^1\text{H}$  NMR  $\delta$ : 4.54 (2H, s), 5.15 (2H, s), 6.81 (1H, d,  $J$  = 8.8Hz), 7.33-7.48 (7H, m)

## 10 General Method 2

Example 1: 1-({5-bromo-2-[(phenylmethyl)oxy]phenyl}methyl)-5-methyl-1*H*-pyrazole-3-carboxylic acid

Example 2: 1-({5-bromo-2-[(phenylmethyl)oxy]phenyl}methyl)-5-methyl-1*H*-pyrazole-5-carboxylic acid



Methyl 1*H*-pyrazole-3-carboxylate (12.61 mg, 0.1 mmol) was dissolved in a 0.105M solution of potassium *tert*-butoxide in ethanol (1ml, 11.78 mg, 0.105 mmol). After stirring at room temperature for 5 mins, a 0.1M solution of 4-bromo-2-(bromomethyl)phenyl phenylmethyl ether in ethanol (1ml, 35.6 mg, 0.1 mmol) was added and the resulting solution was stirred and heated at 60°C under nitrogen for 4hrs. After cooling the mixture was diluted with ethanol (1 ml) and a 0.5M solution of lithium hydroxide in water (1 ml, 11.97mg, 0.5mmol) was added. The mixture was stirred overnight at 40°C. After cooling 2M hydrochloric acid (0.3ml, 0.6mmol) was added and the mixture was diluted with water. Dichloromethane was added and the mixture stirred vigorously. The organic layer was separated and the solvent removed *in vacuo*. The residue was purified by mass directed autopurification to yield the title compounds.

1-({5-bromo-2-[(phenylmethyl)oxy]phenyl}methyl)-5-methyl-1*H*-pyrazole-3-carboxylic acid: (10.7mg, 27.6%).

$^1\text{H}$  NMR  $\delta$ : 5.08 (2H, s), 5.34 (2H, s), 6.72 (1H, d,  $J$  = 2.2Hz), 6.92 (1H, d,  $J$  = 8.8Hz), 7.23 (1H, d,  $J$  = 2Hz), 7.30-7.39 (6H, m), 7.45 (1H, d,  $J$  = 2Hz).

$t$  = 3.38, [MH<sup>+</sup>] 387, 389 [MH<sup>-</sup>] 385, 387.

1-({5-bromo-2-[(phenylmethyl)oxy]phenyl}methyl)-5-methyl-1*H*-pyrazole-5-carboxylic acid (2.3mg, 5.9%).

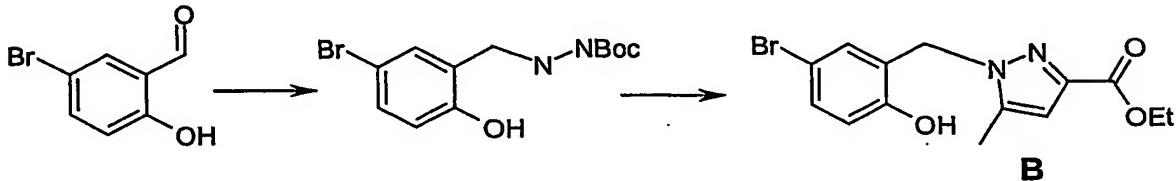
$^1\text{H}$  NMR  $\delta$ : 5.08 (2H, s), 5.83 (2H, s), 6.54 (1H, d,  $J$  = 2.01Hz), 6.80 (1H, d,  $J$  = 8.8Hz), 6.90 (1H, d,  $J$  = 2.01Hz), 7.23-7.38 (6H, m), 7.53 (1H, d,  $J$  = 1.76Hz).

$t$  = 3.66, [MH<sup>+</sup>] 387, 389 [MH<sup>-</sup>] 385, 387.

**General Method 3**

Preparation of ethyl 1-[*(5*-bromo-2-hydroxyphenyl)methyl]-5-methyl-1*H*-pyrazole-3-carboxylate (Intermediate B)

5



a) 1,1-dimethylethyl 2-[*(5*-bromo-2-hydroxyphenyl)methyl]hydrazinecarboxylate

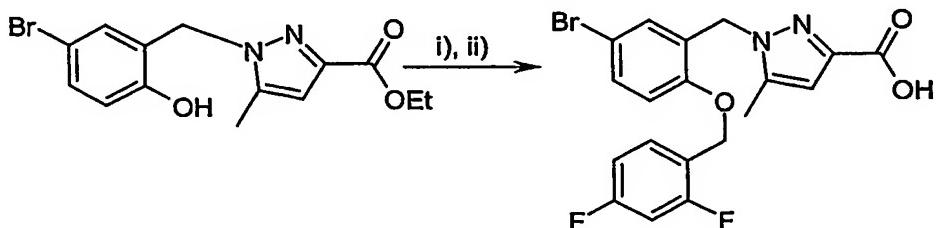
- 10 5-bromo-2-hydroxybenzaldehyde (4.02g, 20mmol) was dissolved in dichloromethane (100ml). *Tert*-butyl carbazate (2.64g, 20mmol) and acetic acid (1.14ml, 1.2g, 20mmol) were added and the mixture was stirred under nitrogen for 30mins. Sodium triacetoxyborohydride (12.72g, 60mmol) was added portionwise and the resulting suspension was then stirred overnight under nitrogen. 2M hydrochloric acid (30ml, 60mmol) was added and the resulting solution was diluted with dichloromethane and water. The organic phase was separated, washed sequentially with brine and water then dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated to dryness to give the title compound as a white solid (6.01g, 94.7%).
- 15  $^1\text{H}$  NMR  $\delta$ : 1.48 (9H, s), 4.13 (2H, s), 4.40 (1H, br s), 6.15 (1H, br s), 6.78 (1H, d,  $J = 8.8\text{Hz}$ ), 7.16 (1H, d,  $J = 2.26\text{Hz}$ ), 7.29-7.32 (1H, m), 9.28 (1H, br s).  $t = 3.11$ ,  $[\text{MH}^+] 317, 319$   $[\text{MH}^-] 315, 317$ .

b) Ethyl 1-[*(5*-bromo-2-hydroxyphenyl)methyl]-5-methyl-1*H*-pyrazole-3-carboxylate (Intermediate B)

- 20 Trifluoroacetic acid (20ml) was added to 1,1-dimethylethyl 2-[*(5*-bromo-2-hydroxyphenyl)methyl]hydrazinecarboxylate (3.2g, 10mmol) in dichloromethane (40ml) and the reaction mixture stirred overnight at room temperature under nitrogen. The solvent was removed in vacuo and the residue obtained redissolved in acetic acid (20ml). The resulting solution was added dropwise to a solution of ethyl 2,4-dioxopentanoate (1.40ml, 1.58g, 10mmol) in acetic acid (10ml) and the reaction mixture was heated at reflux under nitrogen for 1h. The title compound crystallized upon cooling, was filtered, washed with acetic acid and dried under vacuo to give the title compound as white crystals (1.85g, 54.7%).
- 25  $^1\text{H}$  NMR  $\delta$ : 1.39 (3H, t,  $J = 7.15\text{ Hz}$ ), 2.41 (3H, s), 4.34-4.40 (2H, q), 5.18 (2H, s), 6.58 (1H, s), 6.88 (1H, d,  $J = 8.5\text{Hz}$ ), 7.24 (1H, d,  $J = 2.2\text{Hz}$ ), 7.33 (1H, m), 9.56 (1H, br s).  $t = 3.17$ ,  $[\text{MH}^+] 339, 341$   $[\text{MH}^-] 337, 339$ .

**General Method 4**

Example 3: 1-[(5-Bromo-2-[(2,4-difluorophenyl)methyl]oxy)phenyl]methyl]-5-methyl-1*H*-pyrazole-3-carboxylic acid



5

Ethyl 1-[(5-bromo-2-hydroxyphenyl)methyl]-5-methyl-1*H*-pyrazole-3-carboxylate (16.95mg, 0.05mmol) was dissolved in ethanol (0.5ml) and 2M sodium hydroxide (0.0275ml, 0.055mmol) and stirred at room temperature for 5 mins. 1-(bromomethyl)-2,4-difluorobenzene (10.35mg, 0.05mmol) in ethanol (0.5ml) was added and the reaction

10 mixture heated under nitrogen at 70°C overnight. After cooling the mixture was diluted with ethanol (0.5 ml) and a 0.5M solution of lithium hydroxide in water (0.5 ml, 5.99mg, 0.25mmol) was added. The mixture was stirred at 40°C for 3 h. After cooling 2M hydrochloric acid (0.15ml, 0.3mmol) and the mixture was diluted with water. Dichloromethane was added and the mixture stirred vigorously. The organic layer was  
15 separated and the solvent removed *in vacuo*. The residue was purified by mass directed autopurification to yield the title compound (18.4mg, 84.2%).

<sup>1</sup>H NMR δ: 2.13 (3H, s), 5.10 (2H, s), 5.27 (2H, s), 6.55 (1H, s), 6.85 (1H, d, J = 2Hz), 6.89-6.97 (3H, m), 7.36-7.46 (2H, m).

t = 3.48, [MH<sup>+</sup>] 437, 439 [MH<sup>-</sup>] 435, 437.

20

Regioisomers: Elucidation of isolated structures where regioisomers can be formed (general methods 2 and 3) was determined by using either NMBC (heteronuclear multiple bond correlation); nOe (nuclear Overhauser effect) NMR techniques.

The following Examples were prepared from either Intermediate A or Intermediate B and Methods 2 or 4, and other appropriate starting materials.

4		Name	1-(5-bromo-2-[(2,4-dichlorobenzyl)oxy]benzyl)-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR $\delta$ : 2.15 (3H, s), 5.13 (2H, s), 5.31 (2H, s), 6.57 (1H, s), 6.80 (1H, d, $J$ = 2.5Hz), 6.86 (1H, d, $J$ = 8.8Hz), 7.28 (1H, m), 7.35 (1H, m), 7.39 (1H, d, $J$ = 8.3Hz), 7.43 (1H, d, $J$ = 2Hz)
		LCMS	$t$ = 3.84, [MH <sup>+</sup> ] 467, 469, 471 [MH <sup>-</sup> ] 469, 471, 473
		Method	B and Method 4
5		Name	1-(5-bromo-2-[(2,4-difluorobenzyl)oxy]benzyl)-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR $\delta$ : 2.13 (3H, s), 5.10 (2H, s), 5.27 (2H, s), 6.55 (1H, s), 6.85 (1H, d, $J$ = 2Hz), 6.89-6.97 (3H, m), 7.36-7.46 (2H, m)
		LCMS	$t$ = 3.48, [MH <sup>+</sup> ] 437, 439 [MH <sup>-</sup> ] 435, 437
		Method	B and Method 4
6		Name	1-(5-bromo-2-[(4-chlorobenzyl)oxy]benzyl)-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR $\delta$ : 2.16 (3H, s), 5.10 (2H, s), 5.32 (2H, s), 6.57 (1H, s), 6.91 (1H, d, $J$ = 2.2Hz), 6.99 (1H, d, $J$ = 8.8Hz), 7.38-7.40 (5H, m)
		LCMS	$t$ = 3.60, [MH <sup>+</sup> ] 435, 437 [MH <sup>-</sup> ] 433, 435
		Method	B and Method 4
7		Name	1-(5-bromo-2-[(4-fluorobenzyl)oxy]benzyl)-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR $\delta$ : 2.14 (3H, s), 5.09 (2H, s), 5.30 (2H, s), 6.57 (1H, s), 6.92 (1H, d, $J$ = 2Hz), 7.00 (1H, d, $J$ = 8.8Hz), 7.10 (2H, t, $J$ = 8.8Hz), 7.38-7.44 (3H, m)
		LCMS	$t$ = 3.44, [MH <sup>+</sup> ] 419, 421 [MH <sup>-</sup> ] 417, 419
		Method	B and Method 4
8		Name	1-[2-(benzyloxy)-5-bromobenzyl]-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR $\delta$ : 2.16 (3H, s), 5.08 (2H, s), 5.35 (2H, s), 6.67 (1H, s), 6.82-6.86 (2H, m), 7.34-7.43 (6H, m)
		LCMS	$t$ = 3.42, [MH <sup>+</sup> ] 401, 403 [MH <sup>-</sup> ] 399, 401
		Method	B and Method 4

9		Name	1-(5-bromo-2-[(2-chlorobenzyl)oxy]benzyl)-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR $\delta$ : 2.13 (3H, s), 5.17 (2H, s), 5.32 (2H, s), 6.56 (1H, s), 6.80 (1H, d, $J = 2.3\text{Hz}$ ), 6.88 (1H, d, $J = 8.8\text{Hz}$ ), 7.25-7.43 (5H, m)
		LCMS	$t = 3.66$ , [MH+] 435, 437 [MH-] 433, 435
		Method	B and Generic Method 4
10		Name	1-[2-(benzyloxy)-5-bromobenzyl]-1H-pyrazole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR $\delta$ : 5.08 (2H, s), 5.34 (2H, s), 6.72 (1H, d, $J = 2.2\text{Hz}$ ), 6.92 (1H, d, $J = 8.8\text{Hz}$ ), 7.23 (1H, d, $J = 2\text{Hz}$ ), 7.30-7.39 (6H, m), 7.45 (1H, d, $J = 2\text{Hz}$ )
		LCMS	$t = 3.38$ , [MH+] 487, 489 [MH-] 485, 487
		Method	A and Method 2
11		Name	1-(5-bromo-2-[(2-methoxybenzyl)oxy]benzyl)-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR $\delta$ : 2.12 (3H, s), 3.83 (3H, s), 5.10 (2H, s), 5.28 (2H, s), 6.54 (1H, s), 6.85 (1H, d), 6.91-6.96 (3H, m), 7.28-7.35 (3H, m)
		LCMS	$t = 3.52$ , [MH+] 431, 433 [MH-] 429, 431
		Method	B and Method 4
12		Name	1-(5-bromo-2-butoxybenzyl)-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR $\delta$ : 0.96 (3H, t, $J = 7.4\text{Hz}$ ), 1.43-1.52 (2H, m), 1.73-1.80 (2H, m), 2.21 (3H, s), 3.99 (2H, t, $J = 6.4\text{Hz}$ ), 5.28 (2H, s), 6.58 (1H, s), 6.70 (1H, d, $J = 2.2\text{Hz}$ ), 6.78 (1H, d, $J = 8.8\text{Hz}$ ), 7.29-7.32 (1H, m)
		LCMS	$t = 3.55$ , [MH+] 367, 369 [MH-] 365, 367
		Method	B and Method 4
13		Name	1-(5-bromo-2-[(4-(trifluoromethyl)benzyl)oxy]benzyl)-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR $\delta$ : 2.18 (3H, s), 5.23 (2H, s), 5.36 (2H, s), 6.58 (1H, s), 6.91 (1H, d, $J = 2.2\text{Hz}$ ), 7.00 (1H, d, $J = 8.8\text{Hz}$ ), 7.38-7.41 (1H, m), 7.59 (2H, d, $J = 8.3\text{Hz}$ ), 7.68 (2H, d, $J = 8.3\text{Hz}$ )
		LCMS	$t = 3.61$ , [MH+] 469, 471 [MH-] 467, 469
		Method	B and Method 4

14		Name	1-[5-bromo-2-[(2,6-difluorobenzyl)oxy]benzyl]-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR $\delta$ : 2.08 (3H, s), 5.18 (2H, s), 5.21 (2H, s), 6.50 (1H, s), 6.94 (1H, d, $J$ = 2Hz), 7.04 (2H, t, $J$ = 8Hz), 7.14 (1H, d, $J$ = 8.8Hz), 7.43-7.50 (2H, m)
		LCMS	$t$ = 3.43, [MH+] 437, 439 [MH-] 435, 437
		Method	B and Method 4
15		Name	1-[5-bromo-2-[(3-bromobenzyl)oxy]benzyl]-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR $\delta$ : 2.16 (3H, s), 5.08 (2H, s), 5.31 (2H, s), 6.58 (1H, s), 6.85 (1H, d, $J$ = 2.1Hz), 6.89 (1H, d, $J$ = 8.8Hz), 7.24-7.50 (5H, m)
		LCMS	$t$ = 3.64, [MH+] 479, 481, 483 [MH-] 477, 479, 481
		Method	B and Method 4
16		Name	1-[5-bromo-2-[(3-chlorobenzyl)oxy]benzyl]-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR $\delta$ : 2.16 (3H, s), 5.08 (2H, s), 5.31 (2H, s), 6.58 (1H, s), 6.85 (1H, d, $J$ = 2Hz), 6.89 (1H, d, $J$ = 8.8Hz), 7.27-7.36 (5H, m)
		LCMS	$t$ = 3.59, [MH+] 435, 437 [MH-] 433, 435
		Method	B and Method 4
17		Name	1-[5-bromo-2-(pyridin-4-ylmethoxy)benzyl]-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR $\delta$ : 2.23 (3H, s), 5.22 (2H, s), 5.40 (2H, s), 6.61 (1H, s), 6.87-6.89 (2H, m), 7.35-7.38 (1H, m), 7.51 (2H, d, $J$ = 5.27Hz), 8.53 (2H, d, $J$ = 4.52Hz)
		LCMS	$t$ = 2.58, [MH+] 402, 404 [MH-] 400, 402
		Method	B and Method 4
18		Name	1-[5-bromo-2-[(3-methylbenzyl)oxy]benzyl]-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR $\delta$ : 2.12 (3H, s), 2.33 (3H, s), 5.03 (2H, s), 5.29 (2H, s), 6.56 (1H, s), 6.80 (1H, d, $J$ = 2Hz), 6.85 (1H, d, $J$ = 8.8Hz), 7.11-7.25 (4H, m), 7.30-7.33 (1H, m)
		LCMS	$t$ = 3.58, [MH+] 415, 417 [MH-] 413, 415
		Method	B and Method 4

19		Name	1-(5-bromo-2-[(3-nitrobenzyl)oxy]benzyl)-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	
		LCMS	t = 3.39, [MH+] 446, 448 [MH-] 444, 446
		Method	B and Method 4
20		Name	1-[2-(benzyloxy)-5-bromobenzyl]-5-thien-2-yl-1H-pyrazole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR $\delta$ : 5.06 (2H, s), 5.50 (2H, s), 6.74 (1H, d, J = 1.8Hz), 6.88 (1H, d, J = 8.8Hz), 6.95 (1H, s), 7.00-7.02 (2H, m), 7.27-7.34 (6H, m), 7.43 (1H, d, J = 5.0Hz)
		LCMS	t = 3.83, [MH+] 469, 471 [MH-] 467, 469
		Method	A and Method 2
21		Name	1-[2-(benzyloxy)-5-bromobenzyl]-4-fluoro-1H-pyrazole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR $\delta$ : 5.07 (2H, s), 5.23 (2H, s), 6.90 (1H, d, J = 8.8Hz), 7.29-7.40 (8H, m)
		LCMS	t = 3.48, [MH+] 405, 407 [MH-] 403, 405
		Method	A and Method 2

The following intermediates were prepared from the appropriate starting materials according to Method 3.

5

C		Name	ethyl 1-[(5-chloro-2-hydroxyphenyl)methyl]-5-methyl-1H-pyrazole-3-carboxylate
		NMR	$^1\text{H}$ NMR $\delta$ : 1.26 (3H, t, J=6.9Hz), 2.27 (3H, s), 4.24 (2H, q, J=6.9Hz), 5.23 (2H, s), 6.58 (1H, s), 6.64 (1H, s), 6.86 (1H, d, J=8.5Hz), 7.17 (1H, d, J=8.5Hz), 10.18 (1H, s)
		LCMS	t=3.10, [MH+] 295, 297, [MH-] 295, 293
		Method	Method 3
D		Name	ethyl 1-[(2-hydroxy-5-(methyloxy)phenyl)methyl]-5-methyl-1H-pyrazole-3-carboxylate
		NMR	$^1\text{H}$ NMR $\delta$ : 1.39 (3H, t, J=7.2Hz), 2.40 (3H, s), 3.75 (3H, s), 4.37 (2H, q, J=6.9Hz), 5.21 (2H, s), 6.57 (1H, s), 6.70 (1H, d, J=3.0Hz), 6.81 (1H, dd, J=3.0 and 8.9Hz), 7.93 (1H, d, J=8.9Hz), 8.65 – 8.78 (1H, br s)
		LCMS	t=2.83, [MH+] 291, [MH-] 289
		Method	Method 3

E		Name	ethyl 1-[(2-hydroxyphenyl)methyl]-5-methyl-1 <i>H</i> -pyrazole-3-carboxylate
		NMR	$^1\text{H}$ NMR $\delta$ : 1.39 (3H, t, $J=7.2\text{Hz}$ ), 2.40 (3H, s), 4.37 (2H, q, $J=7.2\text{Hz}$ ), 5.25 (2H, s), 6.57 (1H, s), 6.85 – 6.89 (1H, m), 6.99 (1H, dd, $J=7.3$ and 1.0Hz), 7.14 (1H, dd, $J=7.5$ and 1.5Hz), 7.24 (1H, dd, $J=1.8$ and 8.0Hz), 9.22 (1H, s)
		LCMS	$t=2.85$ , [MH+] 261
		Method	Method 3
F		Name	ethyl 1-[(5-fluoro-2-hydroxyphenyl)methyl]-5-methyl-1 <i>H</i> -pyrazole-3-carboxylate
		NMR	$^1\text{H}$ NMR $\delta$ : 1.39 (3H, t, $J=7.2\text{Hz}$ ), 2.40 (3H, s), 4.37 (2H, q, $J=7.2\text{Hz}$ ), 5.20 (2H, s), 6.59 (1H, s), 6.82 (dd, 1H, $J=2.0$ and 7.5Hz), 6.93 (2H, m)
		LCMS	$t=2.92$ , [MH+] 279, 280
		Method	Method 3

The following Examples were prepared from either Intermediate C, D, E or F according to Method 4.

22		Name	1-[(5-chloro-2-[(4-fluorophenyl)methyl]oxy)phenyl]methyl]-5-methyl-1 <i>H</i> -pyrazole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR $\delta$ : 2.16 (3H, s), 5.04 (2H, s), 5.33 (2H, s), 6.67 (1H, s), 6.71 (1H, d, $J=2.5\text{Hz}$ ), 6.87 (1H, d, $J=8.8\text{Hz}$ ), 7.10 (2H, t, $J=8.8\text{Hz}$ ), 7.22 (1H, dd, $J=8.8$ and 2.5Hz), 7.36 (2H, dd, $J=5.3$ and 3.0Hz)
		LCMS	$t=3.37$ , [MH+] 375, 377, [MH-] 373, 375
		Method	C and Method 4
23		Name	1-[(5-chloro-2-[(4-chlorophenyl)methyl]oxy)phenyl]methyl]-5-methyl-1 <i>H</i> -pyrazole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR $\delta$ : 2.15 (3H, s), 5.10 (2H, s), 5.31 (2H, s), 6.57 (1H, s), 6.76 (1H, d, $J=2.5\text{Hz}$ ), 7.03 (1H, d, $J=8.8\text{Hz}$ ), 7.24 (1H, dd, $J=8.8$ and 2.5Hz), 7.35 – 7.40 (4H, m)
		LCMS	$t=3.51$ , [MH+] 391, 393, [MH-] 389, 391
		Method	C and Method 4

24		Name	1-[(5-chloro-2-[(2-chlorophenyl)methoxy]phenyl)methyl]-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR $\delta$ : 2.19 (3H, s), 5.19 (2H, s), 5.40 (2H, s), 6.67 (1H, s), 6.79 (1H, d, $J=2.3\text{Hz}$ ), 6.89 (1H, d, $J=8.8\text{Hz}$ ), 7.22 (1H, dd, $J=8.8$ and $2.3\text{Hz}$ ), 7.30 – 7.32 (2H, m), 7.43 – 7.45 (2H, m)
		LCMS	$t=3.53$ , [MH+] 391, 393, [MH-] 389, 391
		Method	C and Method 4
25		Name	1-[(5-chloro-2-[(2,4-dichlorophenyl)methoxy]phenyl)methyl]-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR $\delta$ : 2.13 (3H, s), 5.20 (2H, s), 5.27 (2H, s), 6.48 (1H, s), 6.85 (1H, d, $J=2.5\text{Hz}$ ), 7.16 (1H, d, $J=8.8\text{Hz}$ ), 7.38 (1H, dd, $J=8.8$ and $2.5\text{Hz}$ ), 7.45 (1H, dd, $J=8.3$ and $2.0\text{Hz}$ ), 7.62 (1H, d, $J=8.3\text{Hz}$ ), 7.71 (1H, d, $J=2.3\text{Hz}$ )
		LCMS	$t=3.75$ , [MH+] 425, 427, 429, [MH-] 423, 425, 427
		Method	C and Method 4
26		Name	1-[(5-chloro-2-[(2,6-difluorophenyl)methoxy]phenyl)methyl]-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR $\delta$ : 2.13 (3H, s), 5.17 (2H, s), 5.27 (2H, s), 6.63 (1H, s), 6.73 (1H, d, $J=2.5\text{Hz}$ ), 6.95 – 7.02 (3H, m), 7.25 (1H, d, $J=2.5\text{Hz}$ ), 7.34 – 7.41 (1H, m)
		LCMS	$t=3.36$ , [MH+] 393, 395, [MH-] 391, 393
		Method	C and Method 4
27		Name	1-[(5-chloro-2-[(2,4-difluorophenyl)methoxy]phenyl)methyl]-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR $\delta$ : 2.17 (3H, s), 5.09 (2H, s), 5.33 (2H, s), 6.66 (1H, s), 6.71 (1H, d, $J=2.5\text{Hz}$ ), 6.86 – 6.94 (3H, m), 7.24 (1H, dd, $J=8.8$ and $2.5\text{Hz}$ ), 7.36 – 7.42 (1H, m)
		LCMS	$t=3.39$ , [MH+] 393, 395, [MH-] 391, 393
		Method	C and Method 4

28		Name	1-(5-chloro-2-[(phenylmethyl)oxy]phenyl)methyl-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR $\delta$ : 2.16 (3H, s), 5.09 (2H, s), 5.36 (2H, s), 6.67 (1H, s), 6.71 (1H, d, $J=2.5\text{Hz}$ ), 6.89 (1H, d, $J=8.8\text{Hz}$ ), 7.21 (1H, dd, $J=8.8$ and $2.5\text{Hz}$ ), 7.36 – 7.43 (5H, m)
		LCMS	$t=3.35$ , [MH+] 357, 359, [MH-], 355, 357
		Method	C and Method 4
29		Name	1-[2-{[(4-fluorophenyl)methyl]oxy}-5-(methyloxy)phenyl]methyl-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR $\delta$ : 2.15 (3H, s), 3.68 (3H, s), 5.01 (2H, s), 5.36 (2H, s), 6.34 (1H, d, $J=2.8\text{Hz}$ ), 6.65 (1H, s), 6.77 (1H, dd, $J=8.8$ and $3.0\text{Hz}$ ), 6.87 (1H, d, $J=8.8\text{Hz}$ ), 7.06 – 7.11 (2H, m), 7.35 – 7.39 (2H, m)
		LCMS	$t=3.20$ , [MH+] 371, [MH-] 369
		Method	D and Method 4
30		Name	1-[2-{[(4-chlorophenyl)methyl]oxy}-5-(methyloxy)phenyl]methyl-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR $\delta$ : 2.17 (3H, s), 3.68 (3H, s), 5.02 (2H, s), 5.37 (2H, s), 6.33 (1H, d, $J=3.0\text{Hz}$ ), 6.66 (1H, s), 6.76 (1H, dd, $J=8.8$ and $3.0\text{Hz}$ ), 6.85 (1H, d, $J=9.0\text{Hz}$ ), 7.32 – 7.38 (4H, m)
		LCMS	$t=3.36$ , [MH+] 387, 389, [MH-] 385, 387
		Method	D and Method 4
31		Name	1-[2-{[(2-chlorophenyl)methyl]oxy}-5-(methyloxy)phenyl]methyl-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR $\delta$ : 2.18 (3H, s), 3.68 (3H, s), 5.16 (2H, s), 5.42 (2H, s), 6.33 (1H, d, $J=3.0\text{Hz}$ ), 6.65 (1H, s), 6.78 (1H, dd, $J=8.8$ and $3.0\text{Hz}$ ), 6.89 (1H, d, $J=9.0\text{Hz}$ ), 7.29 – 7.31 (2H, m), 7.42 – 7.44 (1H, m), 7.47 – 7.49 (1H, m)
		LCMS	$t=3.36$ , [MH+] 387, 389, [MH-] 385, 387
		Method	D and Method 4

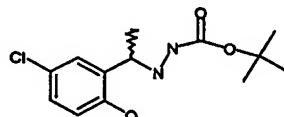
32		Name	1-[{[2-{[(2,4-dichlorophenyl)methyl]oxy}phenyl]methyl}-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR $\delta$ : 2.13 (3H, s), 3.64 (3H, s), 5.12 (2H, s), 5.27 (2H, s), 6.33 (1H, d, $J=3.0\text{Hz}$ ), 6.46 (1H, s), 6.86 (1H, dd, $J=9.0$ and $3.3\text{Hz}$ ), 7.04 (1H, d, $J=8.8\text{Hz}$ ), 7.44 (1H, dd, $J=8.3$ and $2.0\text{Hz}$ ), 7.63 (1H, d, $J=8.3$ ), 7.68 (1H, d, $J=2.0\text{Hz}$ )
		LCMS	$t=3.57$ , [MH+] 421, 423, [MH-] 419, 421
		Method	D and Method 4
33		Name	1-[{[2-{[(2,6-difluorophenyl)methyl]oxy}phenyl]methyl}-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR $\delta$ : 2.12 (3H, s), 3.68 (3H, s), 5.13 (2H, s), 5.30 (2H, s), 6.34 (1H, d, $J=2.8\text{Hz}$ ), 6.61 (1H, s), 6.80 (1H, dd, $J=8.8$ and $3.0\text{Hz}$ ), 6.93 – 7.03 (3H, m), 7.32 – 7.39 (1H, m)
		LCMS	$t=3.20$ , [MH+] 389, [MH-] 387
		Method	I2 and Method 4
34		Name	1-[{[2-{[(2,4-difluorophenyl)methyl]oxy}phenyl]methyl}-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR $\delta$ : 2.10 (3H, s), 3.64 (3H, s), 5.08 (2H, s), 5.20 (2H, s), 6.33 (1H, d, $J=3.0\text{Hz}$ ), 6.46 (1H, s), 6.85 (1H, dd, $J=9.0$ and $3.3\text{Hz}$ ), 7.05 – 7.09 (2H, m), 7.21 – 7.27 (1H, m), 7.56 – 7.62 (1H, m)
		LCMS	$t=3.23$ , [MH+] 389, [MH-] 387
		Method	D and Method 4
35		Name	5-methyl-1-{[5-(methyloxy)-2-[(phenylmethyl)oxy]phenyl]methyl}-1H-pyrazole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR $\delta$ : 2.14 (3H, s), 3.68 (3H, s), 5.06 (2H, s), 5.38 (2H, s), 6.34 (1H, d, $J=2.8\text{Hz}$ ), 6.65 (1H, s), 6.77 (1H, dd, $J=9.0$ and $3.0\text{Hz}$ ), 6.89 (1H, d, $J=9.0\text{Hz}$ ), 7.35 – 7.41 (5H, m)
		LCMS	$t=3.18$ , [MH+] 353, [MH-] 351
		Method	D and Method 4

36		Name	1-[(2-[(4-fluorophenyl)methyl]oxy)phenyl]methyl]-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR $\delta$ : 2.15 (3H, s), 5.15 (2H, s), 5.28 (2H, s), 6.48 (1H, s), 6.76 (1H, d, $J=6.3\text{Hz}$ ), 6.89 – 6.92 (1H, m), 7.11 (1H, d, $J=8.0\text{Hz}$ ), 7.18 – 7.23 (1H, m), 7.25 – 7.29 (1H, m), 7.48 – 7.52 (1H, m)
		LCMS	$t=3.21$ , [MH+] 341, [MH-] 339
		Method	E and Method 4
37		Name	1-[(2-[(4-chlorophenyl)methyl]oxy)phenyl]methyl]-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR $\delta$ : 2.17 (3H, s), 5.08 (2H, s), 5.39 (2H, s), 6.66 (1H, s), 6.77 (1H, d, $J=7.5\text{Hz}$ ), 6.90 – 6.93 (2H, m), 7.24 – 7.26 (2H, m), 7.33 – 7.39 (4H, m)
		LCMS	$t=3.38$ , [MH+] 357, 359, [MH-] 355, 357
		Method	E and Method 4
38		Name	1-[(2-[(2-chlorophenyl)methyl]oxy)phenyl]methyl]-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR $\delta$ : 2.18 (3H, s), 5.21 (2H, s), 5.44 (2H, s), 6.65 (1H, s), 6.77 (1H, d, $J=7.0\text{Hz}$ ), 6.91 – 6.98 (2H, m), 7.26 – 7.32 (3H, m), 7.43 – 7.49 (2H, m)
		LCMS	$t=3.38$ , [MH+] 357, 359, [MH-] 355, 357
		Method	E and Method 4
39		Name	1-[(2-[(2,4-dichlorophenyl)methyl]oxy)phenyl]methyl]-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR $\delta$ : 2.19 (3H, s), 5.17 (2H, s), 5.44 (2H, s), 6.66 (1H, s), 6.76 (1H, d, $J=7.0\text{Hz}$ ), 6.91 – 6.95 (2H, m), 7.25 – 7.31 (2H, m), 7.42 – 7.46 (2H, m)
		LCMS	$t=3.58$ , [MH+] 391, 393, [MH-] 389, 391
		Method	E and Method 4
40		Name	1-[(2-[(2,6-difluorophenyl)methyl]oxy)phenyl]methyl]-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR $\delta$ : 2.12 (3H, s), 5.18 (2H, s), 5.32 (2H, s), 6.61 (1H, s), 6.80 (1H, d, $J=6.5\text{Hz}$ ), 6.91 – 6.99 (3H, m), 7.08 (1H, d, $J=8.3\text{Hz}$ ), 7.29 – 7.39 (2H, m)
		LCMS	$t=3.18$ , [MH+] 359, [MH-] 357
		Method	E and Method 4

41		Name	1-[{(2-(4,4-difluorophenyl)methoxy)phenyl]methyl}-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR $\delta$ : 2.10 (3H, s), 5.16 (2H, s), 5.23 (2H, s), 6.46 (1H, s), 6.79 (1H, d, $J=7.5\text{Hz}$ ), 6.92 – 6.95 (1H, m), 7.09 – 7.18 (2H, m), 7.29 – 7.34 (2H, m), 7.61 – 7.67 (1H, m)
		LCMS	t=3.25, [MH+] 359, [MH-] 357
		Method	E and Method 4
42		Name	5-methyl-1-{[(2-[(phenyl)methoxy)phenyl]methyl}-1H-pyrazole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR $\delta$ : 2.15 (3H, s), 5.11 (2H, s), 5.41 (2H, s), 6.65 (1H, s), 6.78 (1H, d, $J=7.5\text{Hz}$ ), 6.89 – 6.93 (1H, m), 6.97 (1H, d, $J=8.3\text{Hz}$ ), 7.24 – 7.28 (1H, m), 7.36 – 7.42 (5H, m)
		LCMS	t=3.19, [MH+] 323, [MH-] 321
		Method	E and Method 4
43		Name	1-[(5-fluoro-2-{[(4-fluorophenyl)methoxy}phenyl)methyl]-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR $\delta$ : 2.17 (3H, s), 5.04 (2H, s), 5.34 (2H, s), 6.46 (1H, dd, $J=3.0\text{Hz}$ and $8.8\text{Hz}$ ), 6.67 (1H, s), 6.71 (1H, d, $J=2.5\text{Hz}$ ), 6.87 – 6.90 (1H, m), 6.93 – 6.98 (1H, m), 7.08 – 7.12 (2H, m), 7.35 – 7.39 (2H, m)
		LCMS	t=3.23, [MH+] 359, [MH-] 357
		Method	F and Method 4
44		Name	1-[(2-{[(4-chlorophenyl)methoxy}phenyl)methyl]-5-fluorophenyl)-methyl]-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR $\delta$ : 2.18 (3H, s), 5.05 (2H, s), 5.37 (2H, s), 6.42 (1H, dd, $J=3.0$ and $8.5\text{Hz}$ ), 6.67 (1H, s), 6.83 – 6.87 (1H, m), 6.90 – 6.95 (1H, m), 7.32 – 7.39 (4H, m)
		LCMS	t=3.38, [MH+] 375, 377, [MH-] 373, 375
		Method	F and Method 4

45		Name	1-[(2-[(2-chlorophenyl)methyl]oxy)-5-fluorophenyl)methyl]-5-methyl-1 <i>H</i> -pyrazole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR $\delta$ : 2.14 (3H, s), 5.21 (2H, s), 5.34 (2H, s), 6.49 (1H, dd, $J=2.8$ and 8.8Hz), 6.56 (1H, s), 6.98 – 7.08 (2H, m), 7.31 – 7.36 (2H, m), 7.44 – 7.47 (1H, m), 7.49 – 7.51 (1H, m)
		LCMS	$t=3.39$ , [MH $^+$ ] 375, 377, [MH $-$ ] 373, 375
		Method	F and Method 4
46		Name	1-[(2-{[(2,4-dichlorophenyl)methyl]oxy}-5-fluorophenyl)methyl]-5-methyl-1 <i>H</i> -pyrazole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR $\delta$ : 2.13 (3H, s), 5.18 (2H, s), 5.28 (2H, s), 6.48 (1H, s), 6.59 (1H, d, $J=8.8$ Hz), 7.16 (2H, d, $J=5.0$ Hz), 7.46 (1H, dd, $J=8.3$ and 2.0Hz), 7.64 (1H, d, $J=8.3$ Hz), 7.71 (1H, d, $J=2.0$ Hz)
		LCMS	$t=3.59$ , [MH $^+$ ] 409, 411, [MH $-$ ] 407, 409
		Method	F and Method 4
47		Name	1-[(2-{[(2,6-difluorophenyl)methyl]oxy}-5-fluorophenyl)methyl]-5-methyl-1 <i>H</i> -pyrazole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR $\delta$ : 2.13 (3H, s), 5.16 (2H, s), 5.30 (2H, s), 6.46 (1H, dd, $J=8.8$ and 3.0Hz), 6.64 (1H, s), 6.95 – 7.04 (4H, m), 7.34 – 7.41 (1H, m)
		LCMS	$t=3.21$ , [MH $^+$ ] 377, [MH $-$ ] 375
		Method	F and Method 4
48		Name	1-[(2-{[(2,4-difluorophenyl)methyl]oxy}-5-fluorophenyl)methyl]-5-methyl-1 <i>H</i> -pyrazole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR $\delta$ : 2.18 (3H, s), 5.09 (2H, s), 5.35 (2H, s), 6.45 (1H, dd, $J=8.8$ and 2.8Hz), 6.67 (1H, s), 6.86 – 6.98 (4H, m), 7.38 – 7.44 (1H, m)
		LCMS	$t=3.27$ , [MH $^+$ ] 377, [MH $-$ ] 375
		Method	F and Method 4
49		Name	1-({5-fluoro-2-[(phenylmethyl)oxy]phenyl)methyl}-5-methyl-1 <i>H</i> -pyrazole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR $\delta$ : 2.17 (3H, s), 5.08 (2H, s), 5.37 (2H, s), 6.44 (1H, dd, $J=8.8$ and 2.8Hz), 6.67 (1H, s), 6.87 – 6.96 (2H, m), 7.34 – 7.43 (5H, m)
		LCMS	$t=3.22$ , [MH $^+$ ] 341, [MH $-$ ] 339
		Method	F and Method 4

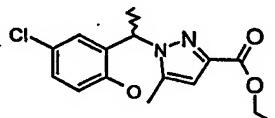
The intermediate 1,1-dimethylethyl 2-[(5-chloro-2-hydroxyphenyl)ethyl] - hydrazinecarboxylate was prepared from the appropriate ketone according to Method 3.



5

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.41 (3H, d, J=6.8Hz), 1.48 (9H, s), 4.21-4.25 (1H, m), 6.23 (1H, br s), 6.77 (1H, d, J = 8.6Hz), 6.96 (1H, d, J = 2.4Hz), 7.11(1H, dd, J=8.6 J=2.3 Hz).

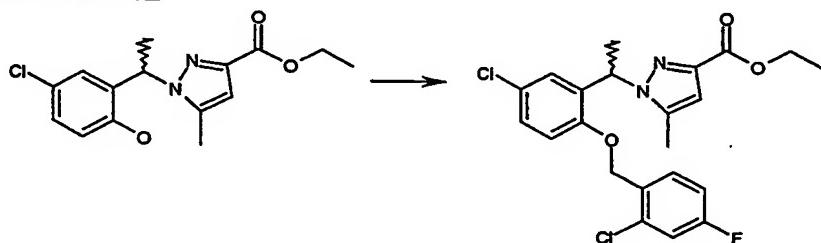
The intermediate 1-[1-(5-chloro-2-hydroxy-phenyl)-ethyl]-5-methyl-1H-pyrazole-3-carboxylic acid ethyl ester (G) was prepared from 1,1-dimethylethyl 2-[(5-chloro-2-hydroxyphenyl)ethyl]hydrazinecarboxylate according to Method 3.



<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.28 (3H, t, J=7.1 Hz), 1.71 (3H, d, J= 6.8 Hz), 2.20 (3H, s), 4.25 (2H, dq, J=2.08 J= 7.1 Hz), 5.81 (1H, q, J=6.8 Hz), 6.56 (1H, s), 6.77 (1H, d, J=2.6 Hz ), 6.84 (1H, d, J=8.6 Hz), 7.14 (1H, dd, J=2.6 J=8.6 Hz), 10.15 (1H, s).

#### General Method 5

1-[1-[5-chloro-2-(2-chloro-4-fluoro-benzyl oxy)-phenyl]-ethyl]-5-methyl-1H-pyrazole-3-carboxylic acid ethyl ester



A mixture of 1-[1-(5-chloro-2-hydroxy-phenyl)-ethyl]-5-methyl-1H-pyrazole-3-carboxylic acid ethyl ester (100mg, 0.32mmol), K<sub>2</sub>CO<sub>3</sub> (112mg, 0.81mmol) and 2-chloro-4-fluorobenzyl bromide (79mg, 0.36mmol) in acetone (3ml) was refluxed overnight under nitrogen. After cooling the solid was filtered off and the solvent removed in vacuo. Purification was carried out on a SPE using iso-hexane containing a gradient of ethyl acetate (5-10%) to yield the title compound (120mg, 74%).

t = 3.95, [MH+] 451,454.

The following 1H-pyrazole-3-carboxylic acid esters were prepared from G according to Method 5

	Name	1-[5-chloro-2-[(2-fluorobenzyl)oxy]-phenyl]-ethyl]-5-methyl-1H-pyrazole-3-carboxylic acid ethyl ester
	LCMS	t = 3.78, [MH+] 417,419
	Method	G and Method 5
	Name	1-[5-chloro-2-[(4-fluorobenzyl)oxy]-phenyl]-ethyl]-5-methyl-1H-pyrazole-3-carboxylic acid ethyl ester
	LCMS	t = 3.77, [MH+] 417,419
	Method	G and Method 5
	Name	1-[5-chloro-2-[(2,4-difluorobenzyl)oxy]-phenyl]-ethyl]-5-methyl-1H-pyrazole-3-carboxylic acid ethyl ester
	LCMS	t = 3.80, [MH+] 435,437 [MH-] 433
	Method	G and Method 5
	Name	1-[5-chloro-2-[(2,4,6-trifluorobenzyl)oxy]-phenyl]-ethyl]-5-methyl-1H-pyrazole-3-carboxylic acid ethyl ester
	LCMS	t = 3.58, [MH+] 453,455
	Method	G and Method 5
	Name	1-[5-chloro-2-[(4-chloro-2-fluorobenzyl)oxy]-phenyl]-ethyl]-5-methyl-1H-pyrazole-3-carboxylic acid ethyl ester
	LCMS	t = 3.96, [MH+] 451,454
	Method	G and Method 5
	Name	1-[5-chloro-2-[(benzyloxy)-phenyl]-ethyl]-5-methyl-1H-pyrazole-3-carboxylic acid ethyl ester
	LCMS	t = 3.77, [MH+] 399,401
	Method	G and Method 5
	Name	1-[1-(5-chloro-2-isobutoxy-phenyl)-ethyl]-5-methyl-1H-pyrazole-3-carboxylic acid ethyl ester
	LCMS	t = 3.88, [MH+] 365,367
	Method	see below

Preparation of 1-[1-(5-chloro-2-isobutoxy-phenyl)-ethyl]-5-methyl-1H-pyrazole-3-carboxylic acid ethyl ester

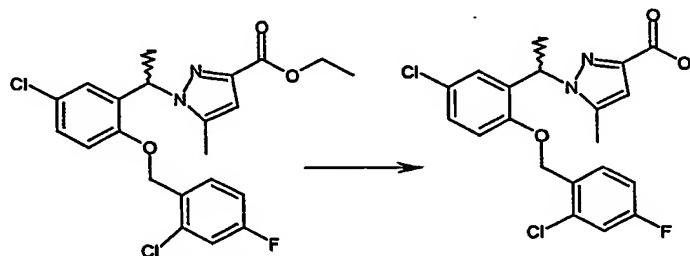
A mixture of 1-[1-(5-chloro-2-hydroxy-phenyl)-ethyl]-5-methyl-1H-pyrazole-3-carboxylic acid ethyl ester (100mg, 0.32mmol),  $K_2CO_3$  (112mg, 0.81mmol) and 1-bromo-2-methylpropane (0.038ml, 0.36mmol) in DMF (3ml) was heated at 80°C under nitrogen for 2 hours. After cooling the solution was diluted with water and extracted with ethyl acetate (3 x 10ml). The combined extracts were dried ( $MgSO_4$ ) and evaporated. Purification was carried out on a SPE ( 20% ethyl acetate :iso-hexane) to yield the title compound.

5  $t = 3.88$ , [MH+] 365,367

## General Method 6

10

Example 50: 1-{1-[5-chloro-2-(2-chloro-4-fluoro-benzyloxy)-phenyl]-ethyl}-5-methyl-1H-pyrazole-3-carboxylic acid



15 To a solution of 1-[1-[5-chloro-2-(2-chloro-4-fluoro-benzyloxy)-phenyl]-ethyl]-5-methyl-1H-pyrazole-3-carboxylic acid ethyl ester (120mg, 0.26mmol) in 3 ml of ethanol and 1ml of water, NaOH (42mg, 1.06mmol) was added. The mixture was stirred at 60°C for 2 hours. the solution was diluted with water, acidified with acetic acid and extracted with ethyl acetate. The organic solution was dried over  $MgSO_4$  and evaporated to give the title

20 compound (112mg, 99%).

25  $^1H$  NMR (DMSO)  $\delta$ : 1.67 (3H, bs), 1.94 (3H, s), 5.21 (2H, s), 5.66 (1H, q,  $J=6.8$  Hz), 6.12 (1H, s), 6.82 (1H, d,  $J=2.6$  Hz), 7.18 (1H, d,  $J=8.8$  Hz), 7.19-7.31 (2H, m), 7.56 (1H, dd,  $J=2.6$   $J=8.8$  Hz), 7.64 (1H, m).

$t = 3.76$ , [MH-] 421, 424.

25

The following Examples were prepared from the appropriate ester intermediate according to Method 6

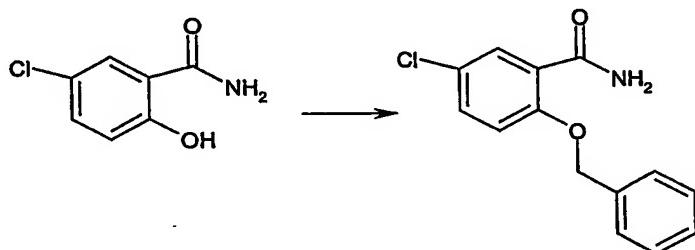
51		Name	1-[5-chloro-2-[(2-fluorobenzyloxy)-phenyl]-ethyl]-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	$^1H$ NMR $\delta$ : (DMSO) 1.68 (3H, d, $J=6.8$ Hz), 2.01 (3H, s), 5.17-5.24 (2H, m), 5.77 (1H, q, $J=6.8$ Hz), 6.43 (1H, s), 6.93 (1H, d, $J=2.6$ Hz), 7.2-7.5 (6H, m), 12.6 (1H,bs).
		LCMS	$t = 3.59$ , [MH+] 389 [MH-] 387, 389
		Method	Method 6

52		Name	1-(5-chloro-2-[(4-fluorobenzyl)oxy]-phenyl)-ethyl]-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR $\delta$ : (DMSO) 1.68 (3H, d, $J=6.8$ Hz), 2.0 (3H, s), 5.17 (2H, s), 5.73 (1H, q, $J=6.8$ Hz), 6.26 (1H, s), 6.88 (1H, d, $J=2.6$ Hz), 7.13 (1H, d, $J=8.8$ Hz), 7.12-7.32 (3H, m), 7.46-7.5 (2H, m).
		LCMS	$t = 3.56$ , [MH+] 3.89 [MH-] 387, 389
		Method	Method 6
53		Name	1-(5-chloro-2-[(2,4-difluorobenzyl)oxy]-phenyl)-ethyl]-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR $\delta$ : (DMSO) 1.66 (3H, d, $J=6.8$ Hz), 2.0 (3H, s), 5.2 (2H, s), 5.63 (1H, q, $J=6.8$ Hz), 6.14 (1H, s), 6.82 (1H, d, $J=2.6$ Hz), 7.12-7.21 (2H, m), 7.28-7.37 (2H, m), 7.60 (1H, q, $J=6.8$ Hz).
		LCMS	$t = 3.61$ , [MH+] 407, 409 [MH-] 405, 407
		Method	Method 6
54		Name	1-(5-chloro-2-[(2,4,6-trifluorobenzyl)oxy]-phenyl)-ethyl]-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR $\delta$ : (DMSO) 1.63 (3H, d, $J=6.8$ Hz), 1.96 (3H, s), 5.14 (2H, q, $J=11$ Hz), 5.65 (1H, q, $J=6.8$ Hz), 6.37 (1H, s), 6.96 (1H, s), 7.25-7.39 (4H, m).
		LCMS	$t = 3.58$ , [MH+] 425, 427 [MH-] 423, 425
		Method	Method 6
55		Name	1-(5-chloro-2-[(4-chloro-2-fluorobenzyl)oxy]-phenyl)-ethyl]-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR $\delta$ : (DMSO) 1.68 (3H, d, $J=6.8$ Hz), 1.97 (3H, s), 5.21 (2H, s), 5.67 (1H, q, $J=6.8$ Hz), 6.18 (1H, s), 6.82 (1H, d, $J=2.6$ Hz), 7.17 (1H, d, $J=8.8$ Hz), 7.24-7.38 (2H, m), 7.50-7.62 (2H, m).
		LCMS	$t = 3.83$ , [MH-] 421
		Method	Method 6
56		Name	1-(5-chloro-2-[(benzyloxy)-phenyl]-ethyl)-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR $\delta$ : (DMSO) 1.68 (3H, bs), 2.1 (3H, s), 5.21 (2H, s), 5.75 (1H, q, $J=6.8$ Hz), 6.2 (1H, s), 6.82 (1H, d, $J=2.6$ Hz), 7.15 (1H, d, $J=8.8$ Hz), 7.21-7.5 (6H, m).
		LCMS	$t = 3.58$ , [MH+] 371
		Method	Method 6

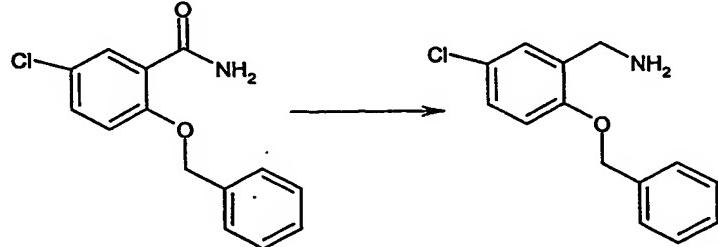
57		Name	1-[1-(5-chloro-2-isobutoxy-phenyl)-ethyl]-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR $\delta$ : (DMSO) 0.98 (6H, t, $J=7.08$ Hz), 1.71 (3H, d, $J=6.88$ Hz), 2.02-2.06 (1H, m), 2.18 (3H, s), 3.80 (2H, d, $J=6.36$ Hz), 5.83-5.87(1H, m), 6.52 (1H, s), 6.85 (1H, d, $J=2.6$ Hz), 7.04 (1H, d, $J=8.8$ Hz), 7.3 (1H, dd, $J=8.7$ , $J=2.6$ Hz), 12.6 (1H, bs).
		LCMS	$t = 3.65$ , [MH+] 337
		Method	Method 6

Preparation of 1-(5-chloro-2-hydroxy-benzyl)-5-methyl-1*H*-pyrrole-3-carboxylic acid ethyl ester (H)

5

Preparation of 2-benzyloxy-5-chloro-benzamide

- 10 A mixture of 5-chloro-2-hydroxy-benzamide (8g, 0.046mol),  $\text{K}_2\text{CO}_3$  (7.72g, 0.056mol) and benzyl bromide (6.1ml, 0.051mol) in acetone (50ml) was refluxed overnight, under nitrogen. After cooling, the solid was filtered off and the filtrate was cooled (in a fridge) to effect crystallisation. The resultant solid was collected to give 9.9g (81%) of a colourless solid.
- 15  $t = 2.90$ , [MH+] 262, 264

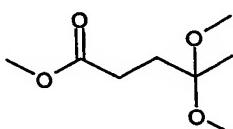
Preparation of 2-benzyloxy-5-chloro-benzylamine

- 20 2-benzyloxy-5-chloro-benzamide (7.9g, 0.030mol) in 20ml of tetrahydrofuran was slowly added, under nitrogen, to a 1M solution of  $\text{LiAlH}_4$  (45ml) in tetrahydrofuran at 0°C. The reaction mixture was then heated at 70°C for 1hour. After cooling the reaction mixture was

5 poured onto water and extracted with ethyl acetate (3 x 40ml). The combined extracts were dried ( $\text{MgSO}_4$ ) and evaporated to give the title compound as a yellow oil (7g, 94%).  
 $^1\text{H NMR } \delta: 1.66$  (2H, bs), 3.84 (2H, s), 5.07 (2H, s), 6.83 (1H, d,  $J=8.6\text{Hz}$ ), 7.15 (1H, dd,  $J=8.6$  and  $2.6\text{Hz}$ ), 7.24-7.42 (6H, m).

5

Preparation of 4,4-dimethoxy-pentanoic acid methyl ester

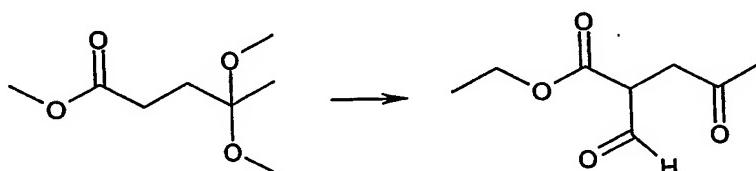


10 Ethyl levulinate (20g, 0.138mol), trimethyl orthoformate (15.3g, 0.144mol) and a catalytic amount of *p*-toluene sulfonic acid monohydrate in 6 ml of methanol were refluxed over the weekend. After cooling the mixture was vacuum down and the residue used with no further purifications.

$^1\text{H NMR } \delta: 1.25$  (3H, bs), 1.94-1.98 (2H, m), 2.32-2.37 (2H, m), 3.17 (6H, s), 3.68 (3H, s).

15

Preparation of 2-formyl-4-oxo-pentanoic acid ethyl ester



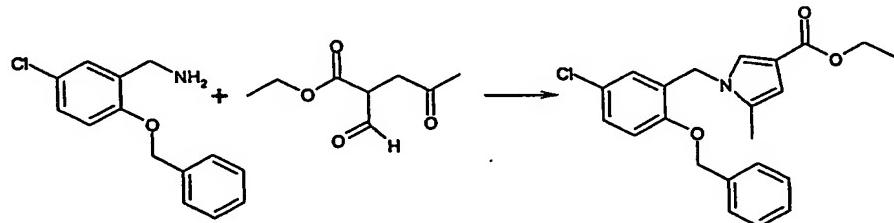
20 A mixture of 4,4-dimethoxy-pentanoic acid methyl ester (25g, 0.13mol) and ethyl formate (21ml, 0.26mol), was added to a solution of NaH (5.78g, 0.144mol) in THF (50ml) at  $\sim 10^\circ\text{C}$ . The reaction mixture was stirred for 3h, then let stand overnight. Water (100ml) and ether (60ml) were added and the mixture stirred for 5 minutes. The organic phase was then separated and washed with water. The combined water layers were acidified to pH2 and extracted with ethyl acetate (3x50ml). The combined extracts were dried ( $\text{MgSO}_4$ ) and evaporated. The residue was then distilled, the fraction with b.p. 110-120°C was the desired compound.

25

$^1\text{H NMR } \delta: 1.27$ -1.32 (3H, m), 2.23 (3H, s), 2.63 (1H, t,  $J=6.7\text{Hz}$ ), 2.76 (1H, t,  $J=6.7\text{Hz}$ ), 3.78-3.81 (1H, m), 4.19-4.28 (2H, m), 9.93 (1H, s).

30

Preparation of 1-(2-benzyloxy-5-chloro-benzyl)-5-methyl-1*H*-pyrrole-3 carboxylic acid ethyl ester



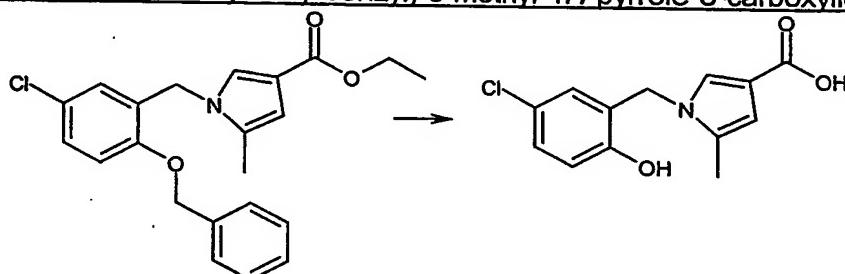
To a mixture of 2-formyl-4-oxo-pentanoic acid ethyl ester (2.5g, 0.016mol) and

2-benzyloxy-5-chloro-benzylamine (4.7g, 0.019mol), CH<sub>3</sub>COOH (~3ml) was added. The reaction mixture was stirred for 2 hours then was poured onto water and extracted with ethyl acetate (3 x 40ml). The combined extracts were dried (MgSO<sub>4</sub>) and evaporated. The residue was purified on a Biotage (15% ethyl acetate:iso-hexane) to give the title

5 compound as a yellow solid (2.8g, 45%).

<sup>1</sup>H NMR δ: 1.32 (3H, t, J=7.1Hz), 2.08 (3H, s), 4.25 (2H, q, J=7.1Hz), 4.98 (2H, s), 5.07 (2H, s), 6.35 (1H, s), 6.61 (1H, s), 6.87 (1H, d, J=8.7Hz), 7.18-7.21 (2H, m), 7.33-7.41 (5H, m).

10 Preparation of 1-(5-chloro-2-hydroxy-benzyl)-5-methyl-1*H*-pyrrole-3-carboxylic acid

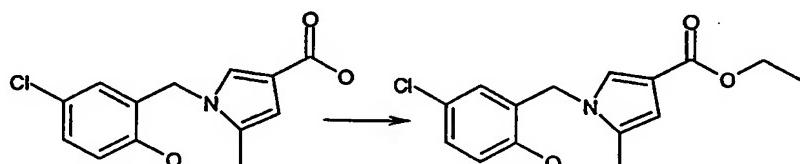


A mixture of sodium methanethiolate (1.16g, 16.5mmol) and 1-(2-benzyloxy-5-chloro-benzyl)-5-methyl-1*H*-pyrrole-3 carboxylic acid ethyl ester

15 (1.27g, 3.3mmol) in DMF(14ml) was stirred at 100°C for 3 hours. After cooling the mixture was diluted with water and acidified with 1M HCl and then extracted with ethyl acetate. The organic phase was dried (MgSO<sub>4</sub>), evaporated to dryness to give the title compound as a yellow oil.

t = 2.76, [MH+] 266 [MH-] 264.

20 Preparation of 1-(5-chloro-2-hydroxy-benzyl)-5-methyl-1*H*-pyrrole-3-carboxylic acid ethyl ester



A mixture of 1-(5-chloro-2-hydroxy-benzyl)-5-methyl-1*H*-pyrrole-3-carboxylic acid (3.3mmol) and H<sub>2</sub>SO<sub>4</sub> (1.5ml) in ethanol (15ml) was refluxed overnight.

25 After cooling the mixture was diluted with water basified with NH<sub>3</sub> and then extracted with ethyl acetate (3x20ml). The combined organic layers were dried (MgSO<sub>4</sub>), and the solvent removed *in vacuo*. Purification was carried out on a SPE using 30% ethyl acetate in iso-hexane to yield the title compound as a yellow solid (0.73g, 75%).  
t = 3.28, [MH+] 294,296 [MH-] 292.

30 The following intermediates were prepared from 1-(5-chloro-2-hydroxy-benzyl)-5-methyl-1*H*-pyrrole-3-carboxylic acid ethyl ester (intermediate H) according to Method 5.

	Name	1-[5-chloro-2-(2-fluoro-benzyloxy)-benzyl]-5-methyl-1H-pyrrole-3-carboxylic acid ethyl ester
	LCMS	t = 3.92, [MH+] 402,404
	Method	H and Method 5
	Name	1-[5-chloro-2-(4-fluoro-benzyloxy)-benzyl]-5-methyl-1H-pyrrole-3-carboxylic acid ethyl ester
	LCMS	t = 3.91, [MH+] 402,404
	Method	H and Method 5
	Name	1-[5-chloro-2-(2,4-difluoro-benzyloxy)-benzyl]-5-methyl-1H-pyrrole-3-carboxylic acid ethyl ester
	LCMS	t = 3.93, [MH+] 420,422
	Method	H and Method 5
	Name	1-[5-chloro-2-(4-chloro-2-fluoro-benzyloxy)-benzyl]-5-methyl-1H-pyrrole-3-carboxylic acid ethyl ester
	LCMS	t = 4.09, [MH+] 436,439
	Method	H and Method 5
	Name	1-[5-chloro-2-(2-chloro-4-fluoro-benzyloxy)-benzyl]-5-methyl-1H-pyrrole-3-carboxylic acid ethyl ester
	LCMS	t = 4.08, [MH+] 436,439
	Method	H and Method 5

The following Examples were prepared from the appropriate ester intermediate according to Method 6.

58		Name	1-[5-chloro-2-(2-fluoro-benzyloxy)-benzyl]-5-methyl-1H-pyrrole-3-carboxylic acid
		NMR	<sup>1</sup> H NMR (DMSO)δ: 1.99 (3H, s), 5.03 (2H, s), 5.23 (2H, s), 6.15 (1H, s), 6.62 (1H, s), 7.21-7.29 (5H, m), 7.36 (1H, d, J=8 Hz), 7.41-7.45 (1H, m), 7.53 (1H, t, J=7.4 Hz), 11.6 (1H, s).
		LCMS	t = 3.50, [MH+] 374,376 [MH-] 372,374
		Method	Method 6
59		Name	1-[5-chloro-2-(4-fluoro-benzyloxy)-benzyl]-5-methyl-1H-pyrrole-3-carboxylic acid
		NMR	<sup>1</sup> H NMR (DMSO)δ: 2.03 (3H, s), 5.07 (2H, s), 5.17 (2H, s), 6.17 (1H, s), 6.64 (1H, s), 7.14-7.23 (3H, m), 7.29 (1H, s), 7.33 (1H, bd), 7.47-7.5 (2H, m), 11.59 (1H, s).
		LCMS	t = 3.48, [MH+] 374,376 [MH-] 372,374
		Method	Method 6

60		Name	1-[5-chloro-2-(2,4-difluoro-benzyl)-benzyl]-5-methyl-1H-pyrrole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR (DMSO) $\delta$ : 1.99 (3H, s), 5.02 (2H, s), 5.19 (2H, s), 6.15 (1H, s), 6.64 (1H, s), 7.08-7.14 (1H, m), 7.21-7.38 (4H, m), 7.58-7.65 (1H, m), 11.6 (1H, s).
		LCMS	t = 3.48, [MH+] 392,394 [MH-] 390,392
		Method	Method 6
61		Name	1-[5-chloro-2-(4-chloro-2-fluoro-benzyl)-benzyl]-5-methyl-1H-pyrrole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR (DMSO) $\delta$ : 2.0 (3H, s), 5.03 (2H, s), 5.21 (2H, s), 6.16 (1H, s), 6.63 (1H, s), 7.21 (1H, d, J=8.8 Hz), 7.28 (1H, s), 7.31-7.37 (2H, m), 7.5-7.58 (2H, m), 11.6 (1H, s).
		LCMS	t = 3.70, [MH+] 408,411 [MH-] 406,410
		Method	Method 6
62		Name	1-[5-chloro-2-(2-chloro-4-fluoro-benzyl)-benzyl]-5-methyl-1H-pyrrole-3-carboxylic acid
		NMR	$^1\text{H}$ NMR (DMSO) $\delta$ : 1.99 (3H, s), 5.06 (2H, s), 5.21 (2H, s), 6.16 (1H, s), 6.63 (1H, s), 7.19-7.28 (3H, m), 7.37 (1H, bd), 7.55 (1H, bd), 7.6-7.68 (1H, m), 11.6 (1H, s).
		LCMS	t = 3.70, [MH+] 408,411 [MH-] 406,409
		Method	Method 6

It is to be understood that the present invention covers all combinations of particular and preferred subgroups described herein above.

5

#### ASSAYS FOR DETERMINING BIOLOGICAL ACTIVITY

The compounds of formula (I) can be tested using the following assays to demonstrate their prostanoid antagonist or agonist activity in vitro and in vivo and their selectivity. The

10 prostaglandin receptors investigated are DP, EP<sub>1</sub>, EP<sub>2</sub>, EP<sub>3</sub>, EP<sub>4</sub>, FP, IP and TP.

#### Biological Activity at EP<sub>1</sub> and EP<sub>3</sub> Receptors

15 The ability of compounds to antagonise EP<sub>1</sub> & EP<sub>3</sub> receptors may be demonstrated using a functional calcium mobilisation assay. Briefly, the antagonist properties of compounds are assessed by their ability to inhibit the mobilisation of intracellular calcium ( $[\text{Ca}^{2+}]_i$ ) in response to activation of EP<sub>1</sub> or EP<sub>3</sub> receptors by the natural agonist hormone prostaglandin E<sub>2</sub> (PGE<sub>2</sub>). Increasing concentrations of antagonist reduce the amount of calcium that a given concentration of PGE<sub>2</sub> can mobilise. The net effect is to displace the

PGE<sub>2</sub> concentration-effect curve to higher concentrations of PGE<sub>2</sub>. The amount of calcium produced is assessed using a calcium-sensitive fluorescent dye such as Fluo-3, AM and a suitable instrument such as a Fluorimetric Imaging Plate Reader (FLIPR). Increasing amounts of [Ca<sup>2+</sup>]<sub>i</sub> produced by receptor activation increase the amount of fluorescence produced by the dye and give rise to an increasing signal. The signal may be detected using the FLIPR instrument and the data generated may be analysed with suitable curve-fitting software.

The human EP<sub>1</sub> or EP<sub>3</sub> calcium mobilisation assay (hereafter referred to as 'the calcium assay') utilises Chinese hamster ovary-K1 (CHO-K1) cells into which a stable vector containing either EP<sub>1</sub> or EP<sub>3</sub> cDNA has previously been transfected. Cells are cultured in suitable flasks containing culture medium such as DMEM:F-12 supplemented with 10% v/v foetal calf serum, 2mM L-glutamine, 0.25mg/ml geneticin and 10µg/ml puromycin.

For assay, cells are harvested using a proprietary reagent that dislodges cells such as Versene. Cells are re-suspended in a suitable quantity of fresh culture media for introduction into a 384-well plate. Following incubation for 24 hours at 37°C the culture media is replaced with a medium containing fluo-3 and the detergent pluronic acid, and a further incubation takes place. Concentrations of compounds are then added to the plate in order to construct concentration-effect curves. This may be performed on the FLIPR in order to assess the agonist properties of the compounds. Concentrations of PGE<sub>2</sub> are then added to the plate in order to assess the antagonist properties of the compounds.

The data so generated may be analysed by means of a computerised curve-fitting routine. The concentration of compound that elicits a half-maximal inhibition of the calcium mobilisation induced by PGE<sub>2</sub> (pIC<sub>50</sub>) may then be estimated.

#### Binding Assay for the Human Prostanoid EP<sub>1</sub> Receptor

Competition assay using [<sup>3</sup>H]-PGE<sub>2</sub>.

Compound potencies are determined using a radioligand binding assay. In this assay compound potencies are determined from their ability to compete with tritiated prostaglandin E<sub>2</sub> ([<sup>3</sup>H]-PGE<sub>2</sub>) for binding to the human EP<sub>1</sub> receptor.

This assay utilises Chinese hamster ovary-K1 (CHO-K1) cells into which a stable vector containing the EP<sub>1</sub> cDNA has previously been transfected. Cells are cultured in suitable flasks containing culture medium such as DMEM:F-12 supplemented with 10% v/v foetal calf serum, 2mM L-glutamine, 0.25mg/ml geneticin, 10µg/ml puromycin and 10µM indomethacin.

Cells are detached from the culture flasks by incubation in calcium and magnesium free phosphate buffered saline containing 1 mM disodium ethylenediaminetetraacetic acid

- ( $\text{Na}_2\text{EDTA}$ ) and  $10\mu\text{M}$  indomethacin for 5 min. The cells are isolated by centrifugation at  $250\text{xg}$  for 5mins and suspended in an ice cold buffer such as  $50\text{ mM Tris}$ ,  $1\text{mM Na}_2\text{EDTA}$ ,  $140\text{mM NaCl}$ ,  $10\mu\text{M}$  indomethacin (pH 7.4). The cells are homogenised using a Polytron tissue disrupter ( $2\times10\text{s}$  burst at full setting), centrifuged at  $48,000\text{xg}$  for 20mins and the
- 5 pellet containing the membrane fraction is washed three times by suspension and centrifugation at  $48,000\text{xg}$  for 20mins. The final membrane pellet is suspended in an assay buffer such as  $10\text{mM 2-[N-morpholino]ethanesulphonic acid}$ ,  $1\text{mM Na}_2\text{EDTA}$ ,  $10\text{mM MgCl}_2$  (pH 6). Aliquots are frozen at  $-80^\circ\text{C}$  until required.
- 10 For the binding assay the cell membranes, competing compounds and [ $^3\text{H}$ ]-PGE<sub>2</sub> ( $3\text{nM}$  final assay concentration) are incubated in a final volume of  $100\mu\text{l}$  for 30 min at  $30^\circ\text{C}$ . All reagents are prepared in assay buffer. Reactions are terminated by rapid vacuum filtration over GF/B filters using a Brandell cell harvester. The filters are washed with ice cold assay buffer, dried and the radioactivity retained on the filters is measured by liquid scintillation
- 15 counting in Packard TopCount scintillation counter.

The data are analysed using non linear curve fitting techniques (GraphPad Prism 3) to determine the concentration of compound producing 50% inhibition of specific binding ( $\text{IC}_{50}$ ).

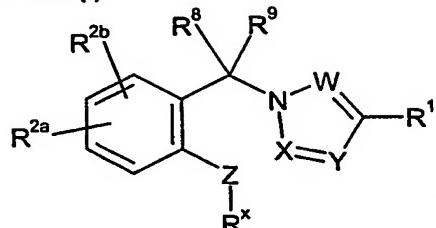
- 20 Biological Activity at TP Receptor
- To determine if a compound has agonist or antagonist activity at the TP receptor a functional calcium mobilisation assay may be performed. Briefly, the antagonist properties
- 25 of compounds are assessed by their ability to inhibit the mobilisation of intracellular calcium ( $[\text{Ca}^{2+}]_i$ ) in response to activation of TP receptors by the stable TXA<sub>2</sub> mimetic U46619. Increasing concentrations of antagonist reduce the amount of calcium that a given concentration of U46619 can mobilise. The net effect is to displace the U46619 concentration-effect curve. The amount of calcium produced is assessed using a calcium-sensitive fluorescent dye such as Fluo-3, AM and a suitable instrument such as a Fluorimetric Imaging Plate Reader (FLIPR). Increasing amounts of  $[\text{Ca}^{2+}]_i$  produced by receptor activation increase the amount of fluorescence produced by the dye and give rise to an increasing signal. The signal may be detected using the FLIPR instrument and the data generated may be analysed with suitable curve-fitting software. The agonist activity
- 30 of the compounds are determined by their ability to cause an increase in intracellular mobilisation in the absence of U46619.
- 35

- The human TP calcium mobilisation assay utilises Chinese hamster ovary-K1 (CHO-K1) cells into which a stable vector containing TP cDNA has previously been transfected.
- 40 Cells are cultured in suitable flasks containing culture medium such as DMEM:F-12 supplemented with 10% v/v foetal calf serum,  $2\text{mM L-glutamine}$ ,  $0.25\text{mg/ml geneticin}$  and  $10\mu\text{g/ml puromycin}$ .

- For assay, cells are harvested using a proprietary reagent that dislodges cells such as Versene. Cells are re-suspended in a suitable quantity of fresh culture media for introduction into a 96-well plate. Following incubation for 24 hours at 37°C the culture media is replaced with a medium containing fluo-3 and the detergent pluronic acid, and a
- 5 further incubation takes place. Concentrations of compounds are then added to the plate in order to construct concentration-effect curves. This may be performed on the FLIPR in order to assess the agonist properties of the compounds. Concentrations of U46619 are then added to the plate in order to assess the antagonist properties of the compounds.
- 10 The data so generated may be analysed by means of a computerised curve-fitting routine. The concentration of compound that elicits a half-maximal inhibition of the calcium mobilisation induced by U46619 ( $\text{pIC}_{50}$ ) may then be estimated, and the percentage activation caused by the compounds directly can be used to determine if there is any agonism present.
- 15 By application of these techniques, compounds of the Examples had an antagonist  $\text{pIC}_{50}$  value of between 7.0 and 10.0 at EP<sub>1</sub> receptors and  $\text{pIC}_{50}$  value of < 5.7 at EP<sub>3</sub> receptors.
- The Examples had antagonist  $\text{pIC}_{50}$  value of between 5.0 and 10.0 at TP receptors.
- 20 No toxicological effects are indicated/expected when a compound (of the invention) is administered in the above mentioned dosage range.
- 25 The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation the following claims:

## CLAIMS

## 1. A compound of formula (I):



(I)

5 wherein:

W represents N or CR<sup>10</sup> wherein R<sup>10</sup> represents hydrogen, halogen, optionally substituted alkyl, optionally substituted aryl, or optionally substituted heterocycl;

X represents N or CR<sup>11</sup> wherein R<sup>11</sup> represents hydrogen, halogen, optionally substituted alkyl, optionally substituted aryl, or optionally substituted heterocycl;

10 Y represents N or CR<sup>12</sup> wherein R<sup>12</sup> represents hydrogen, halogen, CH<sub>3</sub> or CF<sub>3</sub>;

Z represents O, S, SO or SO<sub>2</sub>;

R<sup>1</sup> represents CO<sub>2</sub>R<sup>4</sup>, CONR<sup>5</sup>R<sup>6</sup>, CH<sub>2</sub>CO<sub>2</sub>H, optionally substituted SO<sub>2</sub>alkyl, SO<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>, NR<sup>5</sup>CONR<sup>5</sup>R<sup>6</sup>, 2H-tetrazol-5-yl-methyl or optionally substituted heterocycl;

R<sup>2a</sup> and R<sup>2b</sup> independently represents hydrogen, halo, optionally substituted alkyl,

15 optionally substituted alkoxy, CN, SO<sub>2</sub>alkyl, SR<sup>5</sup>, NO<sub>2</sub>, optionally substituted aryl, CONR<sup>5</sup>R<sup>6</sup> or optionally substituted heteroaryl;

R<sup>x</sup> represents optionally substituted alkyl wherein 1 or 2 of the non-terminal carbon atoms are optionally replaced by a group independently selected from NR<sup>4</sup>, O and SO<sub>n</sub>, wherein n is 0, 1 or 2; or R<sup>x</sup> represents optionally substituted CQ<sup>a</sup>Q<sup>b</sup>-heterocycl, optionally

20 substituted CQ<sup>a</sup>Q<sup>b</sup>-bicyclic heterocycl or optionally substituted CQ<sup>a</sup>Q<sup>b</sup>-aryl;

R<sup>4</sup> represents hydrogen or an optionally substituted alkyl;

R<sup>5</sup> represents hydrogen or an optionally substituted alkyl;

R<sup>6</sup> represents hydrogen or optionally substituted alkyl, optionally substituted heteroaryl, optionally substituted SO<sub>2</sub>aryl, optionally substituted SO<sub>2</sub>alkyl, optionally substituted

25 SO<sub>2</sub>heteroaryl, CN, optionally substituted CQ<sup>a</sup>Q<sup>b</sup>aryl, optionally substituted CQ<sup>a</sup>Q<sup>b</sup>heteroaryl or COR<sup>7</sup>;

R<sup>7</sup> represents hydrogen, optionally substituted alkyl, optionally substituted heteroaryl or optionally substituted aryl;

30 R<sup>8</sup> and R<sup>9</sup> are independently selected from hydrogen, fluorine or alkyl, or R<sup>8</sup> and R<sup>9</sup> together with the carbon to which they are attached form a cycloalkyl ring, optionally containing up to one heteroatom selected from O, S, NH or N-alkyl;

wherein Q<sup>a</sup> and Q<sup>b</sup> are each independently selected from hydrogen, CH<sub>3</sub> and fluorine; or a derivative thereof.